APRIL 1955
VOL. XI NO. 4

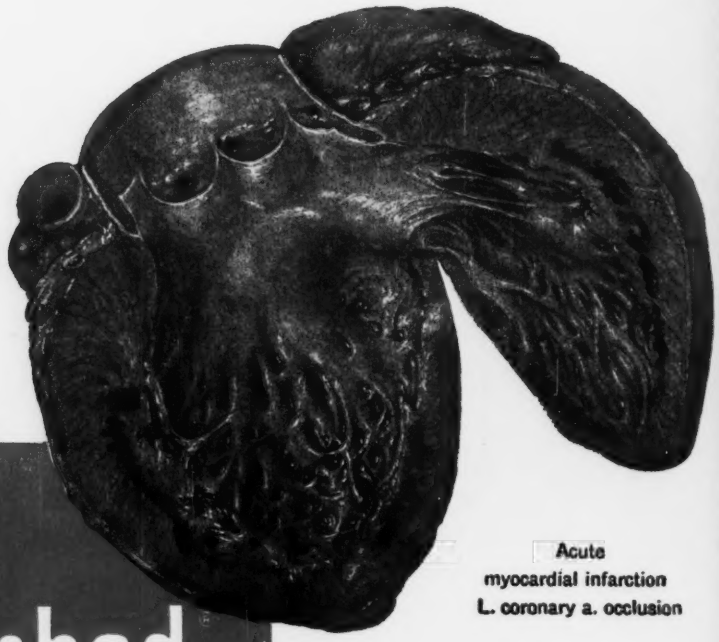
Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Published by Grune & Stratton, Inc.

—in the severe shock

secondary to myocardial infarction



Acute
myocardial infarction
L. coronary a. occlusion

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1. Gazes, P. C., Goldberg, L. I., and Darby, T. D.: *Circulation*, 8: 883, Dec., 1953.

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APRIL 1955
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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Certain Clinical States and Pathologic Changes Associated with Deeply Inverted T Waves in the Precordial Electrocardiogram

By RAYMOND D. PRUITT, M.D., CLAYTON H. KLAKEG, M.D. AND LEMUEL E. CHAPIN, M.D.

A correlation of the clinical and electrocardiographic findings was undertaken in 110 cases which had in common the presence of deeply inverted T waves in central terminal leads centered about position 3 on the precordium. The results of this study are reviewed. A summary is presented of changes encountered at the time of necropsy in nine cases in which electrocardiographic changes of similar type had been recorded. These observations are integrated with concepts derived from the dipole theory. The total evidence is viewed in relation to observations reported by other investigators.

THE T wave of the electrocardiogram always has been a component difficult to deal with. Changes in its configuration occur at times with scant provocation, and even at its normal best, it is commonly upright when, by more simply designed relationships, it should be inverted. In this enlightened period when nearly all things basic in electrocardiography can be crammed into a tight little nutshell of theory, the conduct of the T wave provides a disturbing but intriguing expression of refusal to conform. This stubborn attachment to an individualized, and in some measure unpredictable, performance may justify application of a method which otherwise would be held archaic to a study of one of the more remarkable aberrations of this wave. The proposition basic to the study hereafter reported is that something may be learned about the origins of an electrocardiographic phenomenon by correlating it with the clinical, and in a few instances the pathologic, states in which it appears. Perhaps the argument would bear more weight if certain experiences that led to its projection were recalled.

Over a period of several years, an occasional patient has been encountered who presented few if any symptoms of cardiac disease and yet whose electrocardiogram was so manifestly abnormal that even the undiscerning in matters electrocardiographic would have been alarmed by the changes encountered. The peculiar feature of the electrocardiogram was the presence of deeply inverted T waves in records from precordial leads from all or part of the points between positions 1 and 6.

A 52 year old man came to the Mayo Clinic because of symptoms and findings indicative of polyneuritis. Careful study failed to reveal the cause of his neurologic disease but did disclose an abnormal electrocardiogram characterized by deeply inverted T waves in precordial leads V_2 to V_6 (fig. 1). He presented no symptoms suggestive of angina pectoris or impaired myocardial reserve. Such unusual pathologic processes as periarteritis nodosa and hemochromatosis were considered but discarded as likely diagnostic possibilities. Coronary sclerosis with myocardial infarction was regarded as the most likely basis for the abnormalities in the electrocardiogram, but in the absence of supporting evidence in the patient's clinical state, no definite

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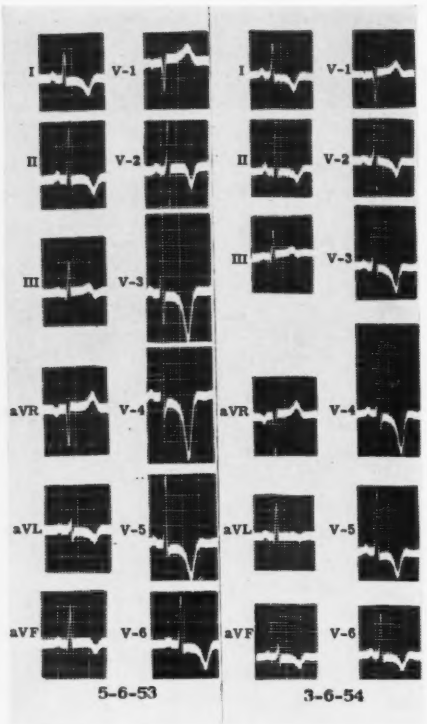

FIG. 1. A 52 year old man presented neither symptoms nor signs of cardiac disease. Note the deeply inverted T waves, particularly in precordial leads V_3 and V_4 and the absence of significant abnormalities in the QRS complexes. This is the kind of electrocardiogram classed as "typical" in this study.

diagnosis was made An electrocardiogram 10 months later disclosed some lessening in the degree of inversion of the T waves but did not differ otherwise from the earlier record. No symptoms of cardiac disease had developed.

Such experiences afforded reason for collecting a group of tracings of this type and establishing a correlation between the electrocardiogram and the pertinent clinical and pathologic data. Records were considered acceptable if the T waves were inverted deeply in precordial lead V_3 and perhaps in leads from positions to the right and left of that point and if no obvious changes in the QRS complexes were present. At the outset, no limits were set for the exact degree of inversion required for inclusion in the series; when the data were analyzed, it was decided to retain all cases, arranging them in the categories to be described.

ANALYSIS OF DATA

The material to be analyzed in this study necessarily must be separated as sharply as possible into two types, namely electrocardiographic evidence and clinical data apart from the electrocardiogram.

Electrocardiographic Data. Approximately half of the electrocardiograms that had been selected during several years were found to have the essential features of the record reproduced in figure 2. The remainder had certain features of these "typical" tracings but failed in one or more ways to satisfy the

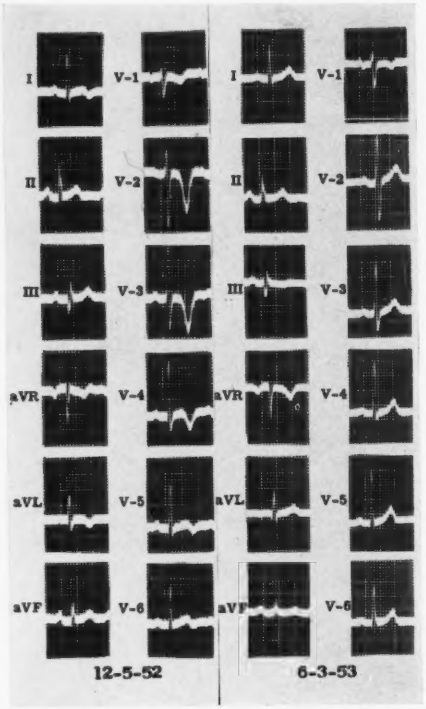

FIG. 2. A 51 year old man had experienced three episodes of severe thoracic pain. The first attack, on November 10, 1952, lasted one hour; the second, on November 24, lasted 20 minutes, and the third and last, on December 4, lasted 15 minutes. The deeply inverted T waves in the tracing of 12–5–52 are unattended by changes in the QRS complexes. In the record of 6–3–53, the deflections in the T waves have reverted to an upright configuration.

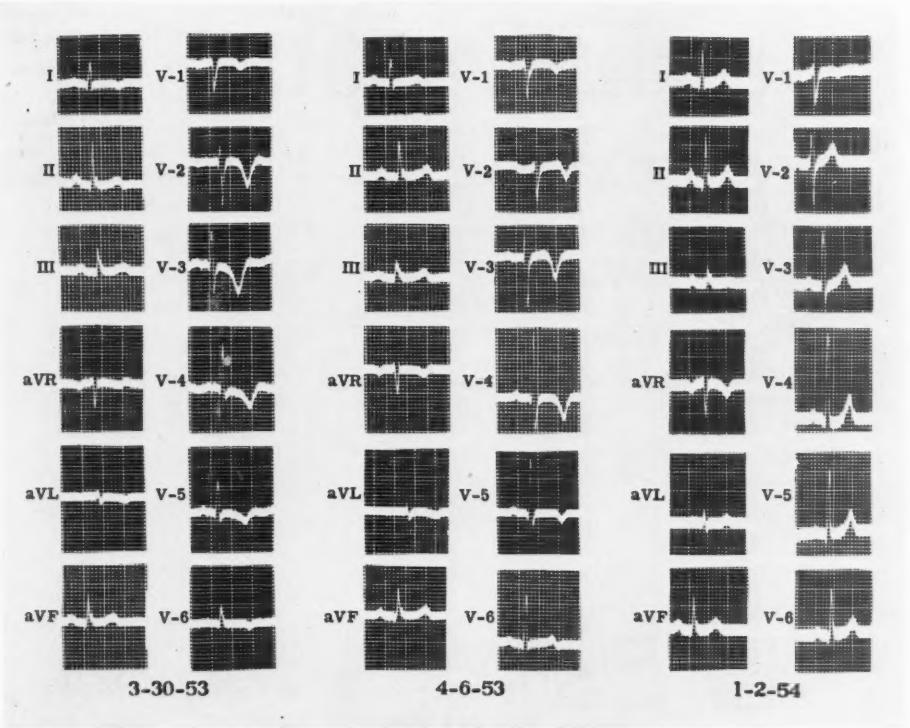

FIG. 3. A 62 year old man had noted episodes of severe thoracic pain two or three times daily for a week prior to the first tracing. These attacks occurred without relation to exertion or emotional disturbances and lasted about 20 minutes. The episodes ceased after the first electrocardiogram. The record of 3–30–53 reveals deeply inverted T waves in precordial leads V_2, V_3 and V_4. A Q wave 1 mm. in depth is present in all precordial leads except V_1. The tracing of 4–6–53 is essentially unchanged; note the notched character of the R deflection in V_2 and the tiny Q waves in leads V_3 through V_6. Both T-wave and QRS changes are gone in the tracing of 1–2–54.

criteria for classification among the typical records. The decision was made to proceed with analysis of these atypical tracings and the clinical records of the patients from whom they were derived, with the hope that some insight would be gained into the significance of deductions made in study of the typical tracings by comparing them with the results derived from study of the less typical records.

With a minimum of segregation, the electrocardiograms were placed in the following five categories:

1. The first group included the typical cases. Of a total of 110 cases in the entire series, 62 were placed in the category of which the record in figure 2 is representative and which might be regarded as the prototype of tracings on which interest had been focused originally. This group of electrocardiograms was characterized by the presence in lead V_3 of a T deflection inverted to a depth of at least 5 mm. and as deeply inverted as the T wave in lead V_5 or more so.

2. In the second category, typical changes in the T wave were associated with some relatively minor change in the QRS complexes (fig. 3). Of the 110 cases, 20 were so classified. In 14 of these cases, this change consisted of a Q wave from 0.5 mm. to 3 mm. in depth in one, two or all of leads V_2, V_3 and V_4. In a single instance, an R wave was present in leads V_1 and V_2 but not in V_3. In another, the

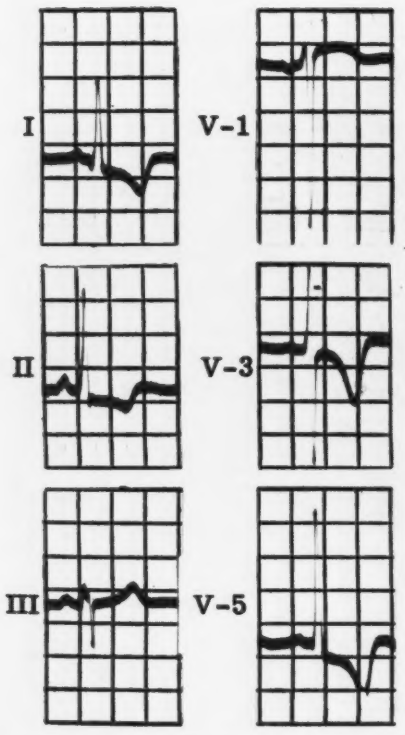

FIG. 4. A 56 year old man presented findings indicative of aortic stenosis. For 10 years he had been subject to angina pectoris; at the time this electrocardiogram was made, he could walk only half a block before his pain appeared. These records are representative of the category designated "left-strain variants" in this study.

R waves in V_2 and V_3 were notched. In four cases, small Q waves, not deeper than 3 mm., were present in standard leads II and III.

3. In the third group, which included 13 of the 110 cases, the R waves in leads V_5 and V_6 were tall and of a kind commonly seen in left ventricular hypertrophy (fig. 4). In many of these 13 cases the T waves in V_5 were more deeply inverted than in V_3 and some measure of depression of the RS-T segment was present in lead V_5. In all cases in this group, the T waves in lead V_3 or V_5 or both were inverted to a depth of at least 5 mm. Because of the obvious relationship to the pattern of left ventricular strain, these cases were identified as "left-strain variants."

4. In the fourth category, which comprised six cases, evidence of delay in the arrival of excitation at the right ventricular surface was associated with changes of a "typical" nature in the T waves (fig. 5). The characteristics of the QRS complexes in this group suggested the presence of right ventricular hypertrophy

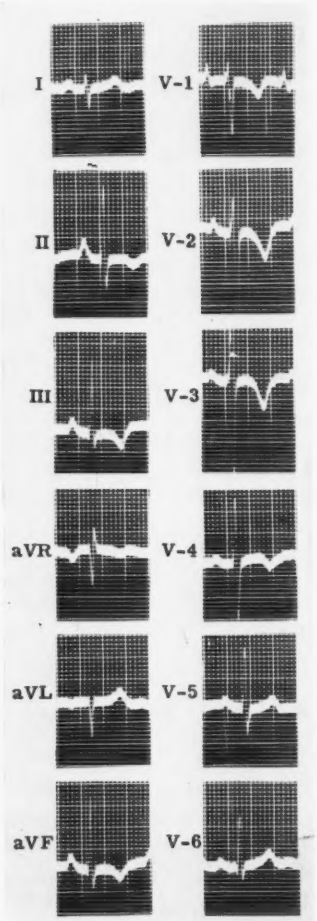

FIG. 5. A 29 year old man had severe bronchiectasis and was in congestive cardiac failure. He died three months after these tracings were recorded but necropsy was not performed. Notable features are the tall P waves in leads II and III, the presence of right axis deviation, the delay in onset of the intrinsicoid deflection in lead V_1 to approximately 0.35 second and the deeply inverted T waves in precordial leads V_1, V_2 and V_3. These tracings are of that group designated "suggestive of right ventricular hypertrophy or of partial or complete right bundle-branch block."

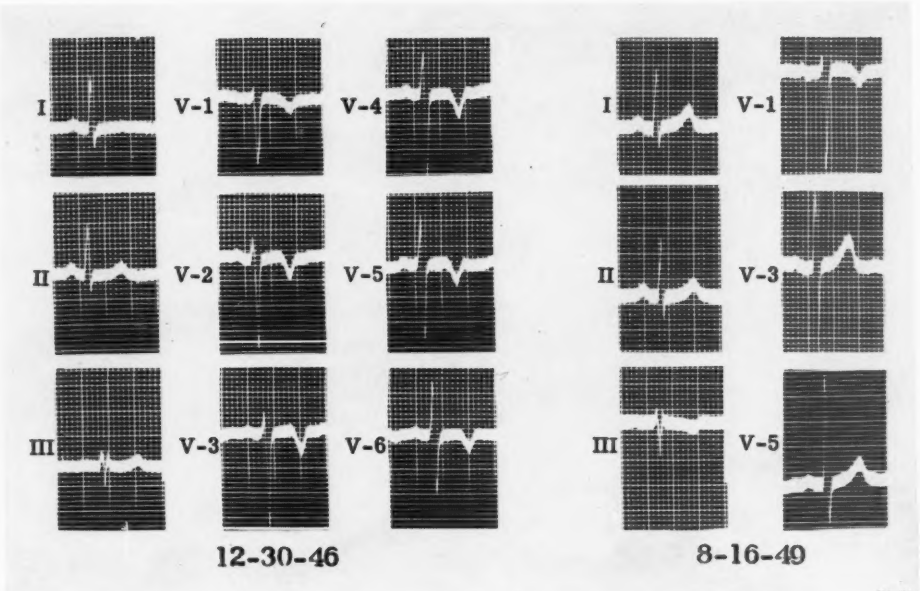

FIG. 6. A 38 year old woman had polycystic disease and moderately severe hypertension. On several occasions between August and October, 1946, she noted anginal distress while walking up a hill. The tracings of 12–30–46 reveal sharp terminal inversion of T deflections in all precordial leads. By 8–16–49 these deflections had reverted to an upright position. These tracings are of that group designated "shallow T-wave inversion" in this study.

or of partial or complete right bundle-branch block.

5. In the final group, the degree of inversion of the T wave in lead V_3 was less than 5 mm. (fig. 6). These nine cases included five that would have been in the "typical" series (group 1) and three that would have been classed as "left-strain variants" (group 3) had the degree of inversion of the T waves been 5 mm. or more.

Clinical Data. Establishment of categories for classification of clinical diagnoses proved a problem as difficult as had that of arranging the electrocardiograms into reasonably homogeneous groups. Because certain clinical diagnoses are of established character and may be used without definition, it was deemed feasible and appropriate to present in tabular form a summary of diagnoses derived from appraisal of the clinical records (see table 1). Of the diagnostic terms used in this table, two deserve clarification with respect to their relationship to each other.

The first is "myocardial infarction," which was applied to the condition of patients who experienced an episode of pain that was severe, lasted an hour or more, and was evidently the occasion, as contrasted with any other in the patient's account, when myocardial injury occurred. The majority of these patients entered the hospital at the acute phase of their illness, and during the first few days they were found to have fever in excess of 100 F. Signs of shock were uncommon even in this group.

The second term is "severe coronary insufficiency," which included the condition of those patients whose episodes of pain varied from mild to severe, commonly lasted less than an hour, and almost always recurred several to many times over periods ranging from a few days to several months. Many of these patients never entered the hospital for treatment, and those who did come in during the acute phase of their illness never exhibited signs of shock nor displayed a significant degree of fever. Some increase in erythrocytic sedimentation rates was commonly present in patients of this

TABLE 1.—*Clinical Correlation With T-wave Changes in Precordial Electrocardiograms*

Clinical Diagnosis	Group (Type of Electrocardiogram)									
	1 ("Typical")		2 (QRS changes)		3 (Left-strain variant)		4 (Right ventricular hypertrophy or right bundle-branch block)		5 (Shallow T-wave inversion)	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Disease of coronary arteries										
Myocardial infarction										
Substantial evidence	9	14	5	25						
Equivocal evidence	5	8			1	8	2	33	2	22
Severe coronary insufficiency										
Substantial evidence	28	45	13	65						
Equivocal evidence	2	3			2	15				
Angina pectoris										
Substantial evidence	5*	8	1	5	6†	46			5‡	56
Equivocal evidence	2	3	1	5	1	8				
Periarteritis nodosa with coronary artery involvement	1	2								
Cardiac disease other than coronary disease										
Hypertension with congestive failure	2	3								
Chronic constrictive pericarditis	1	2								
Aortic valvular stenosis	1	2								
Rheumatic heart disease with mitral stenosis							1	17		
Chronic cor pulmonale							2	33		
Congenital heart disease (A-V commune)							1	17		
Uncomplicated hypertension	3	5			3	23			1	11
No cardiac disease	3	5							1	11
Total	62	100	20	100	13	100	6	100	9	100

* One patient had findings of calcific aortic valvular disease. Another had noted symptoms of severe coronary insufficiency 8 months prior to these electrocardiograms.

† Two patients had severe hypertension, 2 had moderate hypertension, 1 had mild hypertension and 1 had calcific aortic valvular stenosis. One of the 2 with severe hypertension had suggestive myocardial infarction 2 years prior to these electrocardiograms.

‡ Two patients had experienced onset of symptoms within 1 month prior to the electrocardiogram showing inverted T waves. The remaining 3 had nocturnally occurring angina pectoris.

group, as it was in those listed as having myocardial infarction.

Thus, it is evident that the implications of the terms under consideration are of a limited and peculiar character. They refer in each case to a clinical syndrome and no evidence other than that of clinical derivation was adduced in placing patients in one or the other category.

Correlation of Clinical and Electrocardiographic Data. The table records the correlation of clinical and electrocardiographic data. Study disclosed that the several categories of electrocardiograms bear widely differing relationships to the diagnosis of myocardial injury. The full range of variation is represented on the one hand by the tracings designated "QRS changes" and on the other by those categorized as "right ventricular hypertrophy or right bundle-branch block." Among patients whose electrocardiograms fell into the former category, 5 of 20 (25 per cent) had experienced clinical manifestations of myocardial infarction and 13 of 20 (65 per cent) had noted symptomatic expressions of severe coronary insufficiency. In the small group of patients whose

tracings evidenced right ventricular hypertrophy or right bundle-branch block in association with those changes in configuration of T waves characteristic of records included in this study, no patient presented convincing clinical evidence of myocardial injury or of coronary sclerosis.

Between the extremes represented by these two classes of electrocardiograms is that group labeled "typical." This study was designed to ascertain the clinical correlations in this group. The four other categories are included primarily as a means of defining by contrast or by similarity the probable significance of the results obtained in study of the "typical" group. Of the 62 patients in this category, nine (14 per cent) presented other clinical data strongly supporting the diagnosis of myocardial infarction and five (8 per cent) presented equivocal evidence supporting such a diagnosis. The term "equivocal" implies a high degree of qualification in the judgment that could be derived from evidence other than the electrocardiogram. In 28 of the 62 patients (45 per cent), evidence apart from the electrocardiogram supported the diagnosis of severe coronary insufficiency; in two other patients (3 per cent), equivocal evidence for such a diagnosis was elicited. Five of the 62 patients (8 per cent) gave accounts characteristic of angina pectoris and two (3 per cent) presented equivocal histories of such a condition. One patient had periarteritis nodosa attended by clinical evidence and ultimately by evidence at necropsy of involvement of the coronary arteries and focal myocardial scars. Thus, 43 of these 62 patients (69 per cent) presented substantial evidence of disease affecting the coronary arteries. Of these 43 patients, 38 (61 per cent of the total group) had clinical evidence of myocardial infarction or severe coronary insufficiency, and in five others (8 per cent) the diagnosis of angina pectoris was made on purely clinical grounds.

It is of interest that three of the 62 patients in the group whose electrocardiograms showed deeply inverted T waves unattended by changes in the QRS complexes presented absolutely no other clinical evidence of cardiac disease and that three others had no indications of cardiovascular disease apart from uncomplicated hypertension.

An attempt was made to organize such information as was available concerning the duration of a state of deep inversion in the T waves of the precordial electrocardiogram in this category of tracings called "typical." With regard to 25 of the 62 patients in this group, electrocardiograms were obtained over a period in excess of six months or over a period long enough to reveal complete reversal of deeply inverted T waves to an upright position. Of these 25 patients, only 4 failed to show such reversal when records were made over a period in excess of six months. The clinical diagnoses in these four patients and the interval over which deep inversion of T waves was recorded were chronic constrictive pericarditis (18 months), possible aortic stenosis (16 months), polyneuritis with no evidence of cardiac disease (8 months) and hypertension with equivocal evidence of severe coronary insufficiency (15 months). Of the remaining 21 of these 25 patients, one had acute toxic nephritis at the time of the electrocardiogram in which the T waves were inverted; he had made complete recovery when the essentially normal electrocardiogram was recorded seven months later. The other 20 of these 21 patients presented substantial clinical evidence of myocardial infarction or severe coronary insufficiency.

Although nothing resembling a state of statistical purity is claimed for these observations concerning duration of inversion of T waves, the reasonable surmise may be advanced that a transient and reversible state of deep inversion of the T waves of the precordial electrocardiogram bears a high correlation with the existence of clinical data supporting the diagnosis of severe coronary insufficiency or myocardial infarction.

The two remaining categories derived from the electrocardiographic findings, namely the "left-strain variants" and the "shallow T-wave inversions," were similar in that patients with angina pectoris constituted approximately half the total number in each category; no patient whose record included substantial clinical evidence of myocardial infarction or severe

coronary insufficiency was included in either group.

Pathologic Data. Necropsy was done in only 4 of the 62 cases that constituted the "typical" electrocardiographic category. Since evidence obtained from so small a group of cases must necessarily be of most limited extent, the series was augmented by five other cases selected from the files of the Section of Pathologic Anatomy. The electrocardiographic features in these selected cases were similar to those in cases making up the "typical" category.

Healed subendocardial infarction was present in eight of these nine cases. The infarcted regions were predominantly in the lateral wall of the left ventricle in four of these eight, whereas the anterior wall was the site of predominant involvement in three and a small area of healed subendocardial scarring was present in the basal portion of the posterior wall of the left ventricle in the eighth. In the remaining case of these nine, scattered lesions of healed infarction were identified microscopically but no gross scarring was evident. The microscopic lesions were not concentrated in any one portion of the left ventricular wall. A detailed account of these pathologic data will be reported subsequently.

Comment

This study had as its objective a seemingly simple correlation involving clinical data and electrocardiographic findings. To this correlation were to be added, in those few instances in which such data were available, observations on the structural changes in the heart noted at necropsy. But like other studies of modest scope and limited objectives, this one has proved frustratingly difficult.

As already indicated, of the 110 sets of electrocardiograms in the final series, only 62 were classed as typical in the sense that they included the designated abnormalities in configuration of T waves and no other significant electrocardiographic changes. The remaining 48 sets have been distributed among four additional categories based on electrocardiographic characteristics alone. Even the introduction of five categories of electrocardiograms has not permitted achievement of an entirely satisfying degree of conformity among all records placed in a single class. However, to have demanded a greater degree of homogeneity would have led to a hopelessly confusing system of categories; five groups represented solution by compromise.

The other aspect of this ostensibly simple correlation entailed analysis of clinical data. Perhaps the decision should have been made to attempt to determine only whether or not there was evidence of disease affecting the coronary arteries as manifested by angina pectoris or myocardial infarction. This decision often was difficult enough, as indicated by the appreciable number of times that the evidence was rated as equivocal. The effort to distinguish a group of patients whose illness included the usual features of an attack of acute myocardial infarction from a group whose experiences might be related to severe coronary insufficiency may have represented an excessive degree of refinement in diagnostic classification. Admittedly the line of distinction was too faint in certain instances for positive delineation.

With admission of a degree of imperfection, at times distressing, in efforts directed at classification of both the electrocardiographic and the clinical data constituting this study, attention may be turned to such qualified conclusions as may be derived from such data. These conclusions will be developed in the form of answers to certain questions.

Question 1. How reliable an index is deep inversion of the T waves unattended by other significant alteration in the ventricular complex of myocardial infarction or severe coronary insufficiency? As the answer to this question, three sets of figures may be introduced.

a. Thirty-eight of 62 patients (61 per cent) who had "typical" changes in the T wave as the only significant alteration in the electrocardiogram had clinical evidence of myocardial infarction or severe coronary insufficiency.

b. Eighteen of 20 patients (90 per cent) who had not only these characteristic changes in the T waves but also a definite, if minor, abnormality of the QRS complex of a type associated with myocardial injury or scarring presented clinical evidence of myocardial

scarring or severe coronary insufficiency. The significance of this clinicoelectrocardiographic correlation is not its confirmation of what already is generally accepted as electrocardiographic indication of localized myocardial injury; rather, it is the measure it gives of the method used in this study for appraising the clinical data supporting the diagnosis of myocardial infarction or severe coronary insufficiency. The high incidence of supporting clinical evidence in a group of patients having established electrocardiographic evidence of myocardial infarction may be interpreted as indicating the existence of remarkably complete and accurate clinical records on these patients combined with a rather liberal attitude on the part of the investigators as to what constituted adequate support for a clinical diagnosis of myocardial infarction or severe coronary insufficiency.

c. None of the 13 patients whose electrocardiograms were of the type termed "left-strain variant" presented substantial evidence clinically of myocardial infarction or severe coronary insufficiency.

These observations delineate reasonably well the diagnostic implications of an electrocardiogram in which changes in the T wave are "typical." Such changes are not so reliable an index of myocardial injury as is found in a similar tracing in which certain minor alterations in the QRS complex are present but are far more significant in indicating such injury than an electrocardiogram in which changes are those of the kind encountered in the "left-strain variant" group.

One additional observation merits emphasis. In only one patient of the 62 who had "typical" T-wave changes was there incontrovertible evidence of a pathologic process other than coronary insufficiency or myocardial infarction as a basis for the electrocardiographic changes. This patient had chronic constrictive pericarditis and had undergone surgical exploration of the pericardium and heart. It is true that in 23 of these 62 patients the diagnosis of severe coronary insufficiency or myocardial infarction could not be established on clinical grounds, but neither could the presence of such disease be excluded as a basis for the electrocardiographic findings.

Question 2. Does the observation that the deeply inverted T waves revert in time to an upright position alter the diagnostic implications of such a record? As already indicated, in 21 of the 62 patients electrocardiograms were obtained in which such reversal in direction of T waves had occurred. It is re-emphasized that, except for the aforementioned patient who had acute nephritis at the time of the abnormal electrocardiogram, 20 of these 21 patients presented substantial clinical evidence of myocardial infarction or severe coronary insufficiency.

Question 3. Is an electrocardiogram exhibiting "typical" T-wave changes related at all consistently to any particular clinical syndrome of coronary disease? The effort expended in an attempt to answer this question probably exceeded that applied to any other portion of this study, but the answer still must be phrased in qualified terms. The impression derived was that an unusually large proportion of patients in this group presented stories of episodes of severe pain recurring over periods of days or weeks, unattended by shock or fever. As noted previously, for the purpose of this study this syndrome has been termed "severe coronary insufficiency" in contrast to "acute myocardial infarction," the latter diagnosis being applied when the episode or episodes of severe pain occurred within a more limited period and were attended by systemic manifestations of greater consequence. The ratio of patients having severe coronary insufficiency (28) to those having acute myocardial infarction (9) was approximately 3 to 1 in the series with only "typical" T-wave changes. A ratio of this same order was encountered in the series showing in addition to inversion of the T waves minor changes in the QRS complexes indicative of localized myocardial injury. Here, 13 patients were placed in the clinical category of severe coronary insufficiency, whereas to five others was attached a diagnosis of acute myocardial infarction. To conclude that "severe coronary insufficiency" as used in this study is an especially prevalent clinical counterpart among patients showing deeply

inverted T waves in the precordial electrocardiogram attended by minor QRS alterations or by none at all, appears to be reasonably justified.

Question 4. On the basis of such pathologic data as are available, is there a type of myocardial lesion commonly associated with inverted T waves of the kind under consideration in this study? In almost all instances in which necropsy findings are available, subendocardial myocardial infarction in the anterior or lateral wall of the left ventricle has been found.

A Matter of Theory

In a portion of the myocardium where the process of repolarization is prolonged with respect to its duration in other parts, a potential will exist late in electric systole that is negative relative to that existing in other portions of the myocardium. A record derived from an exploring electrode so disposed as to permit recording of changes in potential in that region where repolarization is most delayed will show inversion of the T wave.

Illustration of this principle can be accomplished readily under laboratory conditions where changes of limited character can be wrought in carefully delineated zones, as, for example, by cooling a small region of the epicardium. Application of this same derivative from electrocardiographic theory to an understanding of the alterations in T waves as the latter are encountered clinically is not always so evident. Perhaps no better illustration of this point could be cited than the specific problem of this study, namely the deeply inverted T waves of the precordial electrocardiogram. Exclude from consideration those changes related to ventricular hypertrophy and confine the argument to so-called "primary T-wave changes," and the discussion retains perplexing issues.

Deeply inverted T waves should appear in the precordial electrocardiogram when the process of repolarization in the epicardial myocardium is accomplished later than it is in the endocardial myocardium. A pathologic process that produces a greater degree of injury in the epicardial than in the endocardial fibers is pericarditis. It is true that in the resolving phase of acute pericarditis, T-wave inversions appear in precordial records from points overlying the involved regions. However, coronary disease and not pericarditis was the prevalent pathologic process in this study among patients whose electrocardiograms revealed characteristic inversion of T waves. Study of the changes encountered at necropsy in this series supports the accepted view that coronary disease produces its severest lesions on the endocardial aspect of the left ventricular wall and indicates furthermore that the necrotic tissue commonly is confined to the endocardial half of the left ventricular wall in patients showing only deeply inverted T waves unattended by major changes in the QRS complexes. We may postulate that superficial to these necrotic fibers lay ischemic fibers and that in those nearer the necrotic zone the process of repolarization was retarded to a degree greater than it was in the epicardial fibers. By such reasoning, the T waves in an epicardial lead or in a precordial lead from a point overlying the involved region of the ventricular wall should be upright. But our evidence indicates these deflections were, in fact, inverted.

In an attempt to account for this apparent paradox, an added perspective may be found in the review of sequential records in a case that, from the electrocardiographic standpoint, was unusually well documented. The initial set of electrocardiograms in figure 7 was obtained within a few minutes after the patient began to experience pain in his thorax. In this record, the RS-T segments in precordial leads V_3, V_4 and V_5 were depressed and the T waves were upright and exceedingly large. These alterations are of a kind encountered commonly in the electrocardiograms of patients with coronary disease who are subjected to stress, and it is this type of change that has been said to be characteristic of subendocardial myocardial infarction in previously reported studies of this lesion; in both instances, the ascription of their origin to a boundary so oriented that endocardially disposed myocardial fibers are more severely injured than the more superficially disposed fibers is justified. The transient

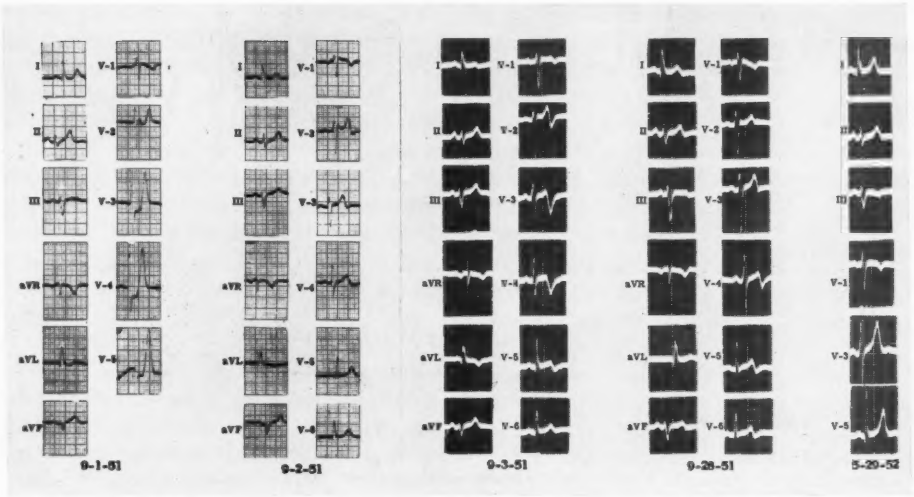

FIG. 7. A 40 year old man experienced severe thoracic pain approximately one hour before the tracing of 9–1–51 was made. Note that in the initial record the RS-T segments are depressed and the T waves are tall and sharply peaked in precordial leads V_3, V_4 and V_5. These features are no longer present in the record of 9–2–51. In the tracing of 9–3–51, the T waves are deeply inverted in precordial leads V_3 and V_4. In the tracing of 9-28-51, these deflections have reverted to a nearly normal configuration; in that of 5–29–52, the resolution is complete. See text for discussion.

character of these changes is illustrated by the fact that in the patient under consideration they were no longer present in an electrocardiogram made approximately two hours after the initial tracing. This second record differed in no discernible way from that dated 9-2-51 in figure 7. In the record dated 9-3-51, approximately 36 hours after the patient first experienced pain, the T wave in precordial leads V_3 and V_4 had become deeply inverted, whereas in the record of 9-28-51 these deflections had returned to a nearly normal configuration.

Let us consider now the contribution that this sequence of electrocardiograms may make to the resolution of the paradox of T-wave inversion in the presence of postulated subendocardial ischemia. In this series of tracings, the initial record was of a type totally consistent with the existence of an acute subendocardial injury overlaid by a zone of ischemic myocardium. An electrocardiogram taken approximately 36 hours later revealed deeply inverted T waves in precordial leads V_3 and V_4, a type of change specific to the interests of this study. What redistribution of boundaries would permit the T waves to undergo so striking a reversal in direction? An answer is suggested in diagrams A and B of figure 8.

In A, representing the initial phase of the electrocardiographic sequence, the boundary of injury *a* is responsible for depression of the RS-T segments in complexes recorded from the electrode *c*. The boundary of ischemia (*b-b*) is the source of those forces producing the tall upright T waves at this same phase. (The lines *a* and, especially, *b-b* symbolize boundaries composed of many layers of myocardial fibers.)

In B, representing the phase of T-wave inversion, the boundary of injury has become stabilized as the fibers in that zone died or recovered sufficiently to become part of the ischemic zone. The voltages arising at that boundary have disappeared from the field. In contrast, the ischemic zone, composed of fibers capable of responding to excitation but characterized still by an abnormality of the process of repolarization, has increased in size and now extends transmurally. The effective boundaries of this ischemic zone now lie at its edges and not in a plane approximating that of the epicardium and endocardium. As a conse-

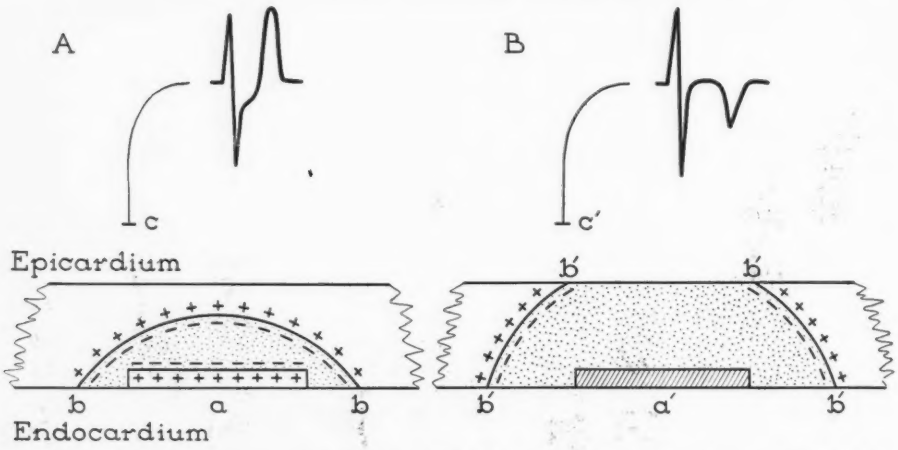

FIG. 8. Diagrammatic representation of the boundaries at which arose the forces responsible for segmental and T-wave aberrations in the series of electrocardiograms reproduced in figure 7. See text for discussion.

quence of this reorientation of boundaries between stages A and B, electrode c' now lies within the negative portion of the electric field and the T waves in a tracing made from this lead will be inverted.*

By this line of argument, the conclusion may be justified that deeply inverted T waves in a direct or semidirect electrocardiographic lead do not, of necessity, imply preponderant epicardial ischemia. Such inversions probably are associated with transmurally disposed regions of ischemia under which a subendocardial zone of myocardial infarction may lie. These inverted T waves are not a consequence of the existence of that infarcted tissue, but our studies, clinical and pathologic, support the conclusion that when characteristic deep inversion of the T waves develops in a patient presenting evidence of severe coronary insufficiency or myocardial infarction, it is a reasonably reliable index that one or more zones of necrotic fibers exist in the subendocardial region. Because of the more enduring character of the T-wave changes as compared with the segmental deviations associated with acute subendocardial myocardial injury, the former may serve more commonly than the latter as an index of the presence of subendocardial myocardial infarction.

* These arguments, as they depend on the significance of forces produced at the edges of a myocardial lesion, are comparable to those advanced in accounting for segmental deviations recorded in the presence of experimentally induced transmural myocardial lesions.[1]

IN PERSPECTIVE AND REFLECTION

Review of numerous publications by Myers and associates has disclosed a scattering of electrocardiograms of the type under consideration. Case 43 of a July, 1950, publication[2] is that of a 15 year old girl with severe hemolytic anemia in whose electrocardiogram deeply inverted T waves were present transiently. At necropsy no myocardial lesions were found, and the changes were ascribed to acute myocardial ischemia secondary to hemolytic anemia. The electrocardiograms of April 4 in case 45 of this same paper were of the type we are concerned with. At necropsy, findings included subacute vegetative aortic valvulitis and widespread miliary abscesses of embolic origin. There was no evidence of myocardial infarction, and gross signs of pericarditis were absent. Microscopically, acute subepicardial myocarditis was present, to which were ascribed the RS-T changes. It might be questioned, however, whether or not the widespread miliary abscesses played a role in the production of these electrocardiographic changes. Case 7 of another 1950 article by Myers[2] is an excellent example of the type of case that poses the

difficult problem of whether or not the inverted T waves can be related solely to the consequences of left ventricular hypertrophy. Case 20 of a third 1950 publication by Myers[2] affords illustration of T wave inversion in leads V_1 through V_4 as a consequence of pulmonary embolism and acute cor pulmonale. This record is distinguished from comparable instances in the present series by the absence of QRS peculiarities in lead V_1 or V_2 of Myers' case and their presence in the records in our series.

Among the series of articles by Myers and associates on myocardial infarction, two illustrations are included of electrocardiograms characterized by deeply inverted T waves. At necropsy, in case 150,[3] findings included an extensive subepicardial lesion that involved the entire lateral wall and overlapped onto the anterior and posterior walls of the left ventricle. Case 125,[4] while complicated by terminal posterolateral infarction, illustrates an instance in which inverted T waves probably were produced by an incident that left multiple small zones of fibrosis in the subendocardial half of the anteroseptal wall of the left ventricle midway between apex and base.

In relation to this latter case, Myers and his coworkers[4] speculated that an electrocardiographic pattern characterized by deeply inverted T waves in precordial leads V_2 and V_4 "brought up the following possibilities: Acute anteroseptal ischemia, a small intramural or subepicardial infarct, acute right ventricular dilatation, and pericarditis." With these speculations we would take no serious issue. However, we would add to this list the possibility of subendocardial infarction of a patchy or confluent type associated with transmural myocardial ischemia and would propose that this was the probable cause of the changes found in this electrocardiogram, as it probably was in many of the cases in our series.

The wariness with which sound clinicians have viewed the general problem of interpretation of changes in the configuration of T waves as an isolated electrocardiographic finding is well represented by Rosenbaum's[5] statements, as he expanded in some measure the earlier comments of Wilson and associates:[6] "The diagnosis of myocardial infarction can be made on the basis of T wave or RS-T segment changes only if a characteristic sequence of alterations, such as shown here, is observed. Even if such a sequence is recorded, it is usually best to be certain that the clinical picture is compatible with the diagnosis. The diagnosis is almost never justified from a single record which shows changes confined to the T waves and RS-T segments. It is probable that infarcts that give rise to changes of this type are relatively small in their extent, or they may be in an unusual location in respect to the type of leading now employed. Most patients with infarcts of this type do well and have no serious impairment of function upon recovery."

Findings in the present study certainly demand no radical revision of this position. Rather our results lend support to every phase of the summary. Perhaps the position of one interpreting such an electrocardiogram is strengthened by the knowledge afforded by the results of this study of what apparently is the largest collection of such records with which medical literature thus far has been encumbered. The present-day "electrocardiographer" is reduced at times to the necessity of laboring over fields that remain unexplored solely by virtue of their total unloveliness.

Summary and Conclusions

1. The presence of deeply inverted T waves in electrocardiograms from central terminal leads centered about position 3 on the precordium unattended by significant changes in the QRS complexes in tracings derived from these or other leads was related in 38 of 62 patients (61 per cent) to clinical evidence of myocardial infarction or severe coronary insufficiency.

2. A transient and reversible state of deep inversion in the T waves obtained from these same leads bears an exceedingly high correlation with the presence of data supporting the diagnosis of severe coronary insufficiency or myocardial infarction.

3. "Severe coronary insufficiency," as used in this study to describe a clinical state differing in some respects from the usual symptomatic manifestations of acute myo-

cardial infarction, was an especially prevalent clinical counterpart of electrocardiograms of the type noted in the first paragraph of this summary.

4. In almost all cases in which necropsy findings were available and in which electrocardiograms had shown deformities of the kind under consideration, subendocardial myocardial infarction was found in the anterior or lateral wall of the left ventricle.

5. Expressed in terms of the dipole theory, deeply inverted T waves of the kind described in this study are commonly an expression of the presence of a transmurally disposed region of myocardial ischemia under which there may be a subendocardial zone of myocardial infarction.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

1. Esseva interprendite un correlation del constatationes clinic e electrocardiographic in 62 casos (seligite ex un serie de 110 casos), que habeva in commun le tracto de undas T a inversion profunde in derivationes terminal central concentrate circa le position 3 del precordio sed nulle cambiamentos significative del complexos QRS in iste o altere derivationes. In 38 inter le 62 casos (61 pro cento), le presentia de undas T a inversion profunde esseva associate con evidentia clinic de infarcimento myocardiac o sever insufficientia coronari.

2. Transientia o reversibilitate del profunde inversion del undas T in iste derivationes occurreva in altissime correlation con datos supportante le diagnose de sever insufficientia coronari o infarcimento myocardiac.

3. "Sever insufficientia coronari"—que se interpreta in iste studio como un stato clinic differente in alicun respectos ab le usual manifestationes symptomatic de acute infarcimentos myocardiac—esseva un facto clinic prevalentissimemente associate con electrocardiogrammas del typo describite in le prime paragrapho de iste summario.

4. In quasi omne casos in que observationes necroptic esseva obtenite e in que le electrocardiogrammas habeva exhibite deformitates del typo sub consideration, infarcimentos myocardiac subendocardiac esseva trovate in le pariete anterior o lateral del ventriculo sinistre.

5. Exprimite in le terminos del theoria dipolic undas T a inversion profunde del typo describite in iste studio es generalmente indicative del presentia de un region de ischemia myocardiac in disposition transmural sub le qual se trova possibilemente un zona subendocardiac de infarcimento myocardiac.

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Mechanical and Myocardial Factors in Rheumatic Heart Disease with Mitral Stenosis

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Sixteen patients with rheumatic heart disease and pure mitral stenosis, studied by cardiac catheterization, are presented to illustrate the relative importance of mitral block and myocardial insufficiency in this disease. Analysis of hemodynamic data permitted a separation of those patients with predominantly mechanical mitral block from those in whom myocardial insufficiency appeared to be the predominant lesion. The importance of recognizing the existence of the latter group is emphasized, since commissurotomy will not be of benefit in such cases.

CIRCULATORY dysfunction in rheumatic heart disease has long been recognized as springing from at least two main sources, the mechanical difficulties imposed by valvular lesions and the insufficiency of the myocardium itself. This insufficiency may result from longstanding strain inflicted on the cardiac muscle by altered valvular function or, independently of mechanical cause, may occur consequent to intrinsic myocardial damage from the rheumatic process. Our understanding of cardiac function in rheumatic patients would be increased if one could separate the mechanical from the myocardial components in order to investigate further the disability these subjects experience. The surgical approach to rheumatic mitral stenosis, attacking as it does only the mechanical features of valvular lesions, affords an opportunity to study this problem. Furthermore, if it can be shown that myocardial insufficiency exists as a separate dysfunction, it behooves the physician and surgeon to be certain that the prospective candidate for mitral commissurotomy is suffering from a predominantly mechanical lesion, namely block at the mitral valve, and not chiefly from myocardial insufficiency. A number of reports have been published discussing the element of mechanical valvular block and its hemodynamic characteristics. In some instances block has been clearly demonstrated by post-commissurotomy hemodynamic studies.[1-5] On the other hand, the predominance of myocardial insufficiency in patients with mitral stenosis and particularly the fact that it can occur without the existence of any significant mechanical block at the mitral valve, has not been stressed from a hemodynamic point of view.

As a result of studies, using the cardiac catheterization technique, made in a series of patients with mitral stenosis who were being considered for mitral surgery, two groups of individuals have emerged whose clinical and physiologic findings have led us to the conclusion that in one the predominant difficulty was due to mechanical block, while in the other it resulted from myocardial insufficiency. The substance of this report is concerned with a presentation and differentiation of the findings in these two groups. It should be emphasized that these individuals were specifically selected to illustrate the *predominance* of one or the other dysfunction, although it was recognized that in any one rheumatic subject these dysfunctions may coexist equally or in varying proportions. Our complete experience with mitral surgery will be reported more fully in a following communication.

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The work described in this paper was supported by a grant from the Life Insurance Medical Research Fund, and by a research grant (PHS Grant H-833(C)) from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

TABLE 1.—*Physiologic Data in 8 Patients with Rheumatic Mitral Stenosis and Predominantly Mitral Block*

Case, Sex, Age	Diagnosis	Time		Cardiac Output (L/min.)	Cardiac Index (L/min./M² BSA)	Heart Rate (beats/min.)	Oxygen Consumption (cc/min./M² BSA)	R.Q.	AV Diff. (vol. %)	Arterial Blood Oxygen		Pressures in mm. Hg			TBV (cc/M² BSA)	PV (cc/M² BSA)	H'crit. (%)
										cont. (vol. %)	sat. (%)	Systemic artery s/d, m	Pulmonary artery s/d, m	Right ventricle d			
Normal					3.12	72	131	0.80	4.2		96	120/79, 90	<30/10, 15	<5	2750	1500	45
*567. JC., M. 35 yrs.	EH. MS. (T.I.) AF. IIC.	Pre-op.	(R)	3.32	1.94	60	124	0.83	6.4	16.6	93	89/66, 75	54/29, 37	5	3338	1905	43
			(E)	3.73	2.21	80	197	0.89	8.9	17.3	96	114/81, 94	81/43, 54	8	—	—	—
		Post-op.															
		1 month	(R)	4.00	2.35	52	125	0.87	5.3	15.9	96	84/56, 66	41/14, 24	2	3350	2010	40
			(E)	4.38	2.58	60	178	0.89	6.9	15.9	96	101/61, 79	61/27, 39	3	—	—	—
		11 months	(R)	4.08	2.28	52	130	0.75	5.7	17.2	93	113/71, 88	35/18, 23	5	3222	1788	45
			(E)	6.26	3.50	88	322	0.82	9.2	17.2	93	124/76, 93	61/27, 40	6	—	—	—
*595. AB., M. 28 yrs.	EH. MS. AI. NSR. IIC.	Pre-op.	(R)	3.85	2.32	68	119	0.85	5.1	19.2	96	113/68, 80	38/16, 24	4	2920	1470	50
			(E)	5.24	3.16	86	237	0.92	7.5	20.1	98	130/69, 92	61/31, 44	9	—	—	—
		Post-op.															
		1 month	(R)	4.98	2.98	74	134	0.89	4.5	17.4	97	120/60, 83	30/12, 20	6	2885	1580	45
			(E)	5.91	3.54	86	244	0.87	6.9	17.1	96	134/63, 94	45/18, 32	10	—	—	—
		12 months	(R)	3.87	2.26	68	116	0.78	5.1	20.6	95	109/59, 78	23/9, 13	4	2760	1316	52
			(E)	5.55	3.25	88	315	0.82	9.7	21.1	97	117/66, 86	25/12, 17	5	—	—	—
*618. HI., F. 41 yrs.	EH. MS. (T.I.) AF. IIC.	Pre-op.	(R)	4.25	2.61	82	138	0.83	5.3	15.8	95	128/78, 101	68/29, 46	8	3560	2095	41
		Post-op.															
		1 month	(R)	4.63	2.84	84	136	0.86	4.8	15.2	95	126/72, 90	55/23, 34	6*	3040	1875	38
*663. LS., F. 37 yrs.	EH. MS. NSR. IIC.	Pre-op.	(R)	3.90	2.80	85	137	0.78	4.9	17.1	97	123/70, 93	46/26, 33	5	2563	1507	41
		Post-op.															
		1 month	(R)	4.55†	3.11†	80	181†	0.78	5.8	13.5	98	122/77, 97	46/21, 35	—	2827	1875	34
		12 months	(R)	3.82	2.63	64	132	0.84	5.0	16.4	98	140/79, 115	32/18, 23	—	2458	1488	39
			(E)	3.55	2.45	68	161	0.84	6.6	16.3	97	146/79, 112	45/23, 31	—	—	—	—
*703. MA., F. 53 yrs.	EH. MS. (G-S) NSR. IIIC.	Pre-op.	(R)	—	—	78	—	—	—	14.8	91	140/80, 100	118/44, 71	5	3203	1890	41
		Post-op.															
		6 months	(R)	3.80	2.28	66	111	0.87	4.9	16.5	98	151/76, 104	83/37, 58	4	2947	1585	46
*707. CC., M. 36 yrs.	EH. MS. (G-S) SA. IIC.	Pre-op.															
		1st Study	(R)	4.68	2.71	78	135	0.93	5.0	15.4	91	128/71, 90	77/32, 45	5	2897	1726	40
		2 weeks	(R)	4.40	2.49	60	127	0.88	5.1	15.9	94	124/68, 86	64/27, 43	5	2850	1602	40
		later	(E)	4.87	2.75	89	253	0.86	9.2	16.3	95	132/74, 95	94/44, 65	12	—	—	—
		Post-op.															
		1 month	(R)	4.23	2.47	56	129	0.82	5.2	17.6	98	120/60, 87	32/14, 22	2	3284	1752	47
			(E)	5.48	3.21	70	208	0.89	6.5	17.3	96	118/60, 83	40/17, 26	4	—	—	—
*714. RD., M. 29 yrs.	EH. MS. SA. IIC.	Pre-op.	(R)	4.11	2.21	64	124	0.79	5.6	17.6	96	129/71, 90	50/18, 30	6	2570	1488	42
			(E)	5.26	2.83	124	275	0.88	9.7	17.9	97	160/91, 112	89/40, 62	11	—	—	—
		Post-op.															
		1½ months	(R)	5.68	3.14	79	138	0.83	4.4	15.1	96	133/71, 94	38/15, 25	—	2820	1731	39
			(E)	7.15	3.95	118	296	0.90	7.5	15.5	97	150/83, 105	55/29, 40	4	—	—	—
*713. EW., F. 28 yrs.	EH. MS. (G-S) NSR. IIID.	Pre-op.	(R)	3.51	2.35	88	120	0.85	5.1	13.0	94	110/65, 80	81/41, 58	3	2742	1725	37
		Post-op.															
		12 months	(R)	4.83	3.16	64	133	0.83	4.2	15.8	97	111/67, 86	25/8, 16	2	2487	1558	37
			(E)	6.43	4.20	91	265	0.89	6.3	16.2	96	123/70, 95	38/18, 28	3	—	—	—

* Read on right atrial curve
† Not in basal state
M²BSA = per square meter of body surface area
AV. diff. = arteriovenous oxygen difference
RQ = respiratory quotient
TBV = total blood volume
PV = plasma volume
H'crit = hematocrit
(R) = at rest
(E) = during exercise
s = systolic
d = diastolic
m = mean
EH = enlarged heart
MS = mitral stenosis
(G-S) = Graham-Steell murmur
NSR = normal sinus rhythm
AF = atrial fibrillation
(T.I.) = tricuspid insufficiency
SA = sinus arrhythmia
AI = aortic insufficiency

Material and Methods

Sixteen patients with mitral stenosis have been selected for presentation in this report. Their diagnoses can be found in tables 1 and 2 and conform to accepted criteria.[7] Three of the subjects, (cases 703, 707, 713, table 1) with a basal diastolic murmur were thought to have pulmonic incompetence with the murmur of Graham-Steell (indicated by bracketed letters G–S) because of the severity of pulmonary hypertension and the absence of left ventricular enlargement or confirmatory evidence of aortic regurgitation. In another three patients (cases 595, table 1; 591, 699, table 2) with a basal diastolic murmur, aortic insufficiency was diag-

TABLE 2—*Physiologic Data in 8 Patients with Rheumatic Mitral Stenosis and Predominantly Myocardial Insufficiency*

Case, Sex, Age	Diagnosis	Time	Cardiac Output (L/min.)	Cardiac Index (L/min./M² BSA)	Heart Rate (beats/min.)	Oxygen Consumption (cc/min./M² BSA)	R.Q.	AV Diff. (vol. %)	Arterial Blood Oxygen		Pressures in mm. Hg			TBV (cc/M² BSA)	PV (cc/M² BSA)	H'crit. (%)
									cont. (vol. %)	sat. (%)	Systemic artery s/d, m	Pulmonary artery s/d, m	Right ventricle d			
Normal				3.12	72	131	0.80	4.2		96	120/70, 90	<30/10, 15	<5	2750	1500	45
#699. FB., M. 27 yrs.	EH. MS. AI. AF. IIC.	Pre-op. (R)	5.08	2.90	67	139	0.77	4.8	15.3	96	129/75, 95	32/18, 24	—	3443	2064	40
		1st study (E)	—	—	80	190	0.77	—	15.6	96	137/76, 95	39/22, 28	—	—	—	—
		2 weeks (R)	5.33	3.04	69	140	0.85	4.6	16.0	95	118/71, 87	28/13, 18	2	3115	1800	42
		later (E)	5.67	3.24	96	194	0.87	6.0	16.0	94	125/77, 93	31/16, 23	2	—	—	—
		Post-op.														
		6 months (R)	4.23	2.46	68	128	0.84	5.2	17.5	98	133/76, 96	25/11, 19	1	3245	1756	46
		(E)	4.40	2.56	83	179	0.87	7.0	17.5	98	132/76, 95	32/16, 22	1	—	—	—
#695. SB., F. 44 yrs.	EH. MS. Atr. Flutter IIIC.	1st study (R) in CHF	2.56	1.48	115	117	0.81	7.9	16.1	91	128/90, 105	32/22, 26	—	3150	1698	46
	EH. MS. NSR. IB.	6 weeks (R) later	3.44	2.08	67	110	0.80	5.3	17.4	99	138/67, 93	27/12, 18	2	2474	1400	43
		18 months (R)	3.42	1.98	64	105	0.79	5.3	15.9	97	125/63, 86	27/16, 20	4	2321	1462	37
		later (E)	3.92	2.27	76	188	0.95	8.3	16.0	98	133/65, 90	30/15, 21	3	—	—	—
#635. GB., M. 39 yrs.	EH. MS. AF. IIC.	Pre-op. (R)	3.50	1.85	54	122	0.81	6.6	18.3	97	106/56, 75	28/16, 20	4	3475	1935	44
		(E)	4.20	2.22	82	209	0.87	9.4	18.3	97	129/86, 103	49/28, 36	5	—	—	—
		Post-op.														
		1 month (R)	3.65	1.95	70	117	0.94	6.0	16.8	97	129/80, 92	28/15, 21	4	2880	1695	34
		(E)	4.64	2.48	100	209	0.82	8.4	16.5	95	150/92, 115	48/28, 37	6	—	—	—
#675. JH., M. 41 yrs.	EH. MS. AF. IIC.	1st study (R)	5.98	3.46	72	149	0.84	4.3	15.3	97	131/76, 100	28/12, 21	4	2735	1678	39
		(E)	6.65	3.84	82	238	1.06	6.2	15.5	97	139/77, 101	39/18, 27	5	—	—	—
#591. NG., M. 28 yrs.	EH. MS. NSR. IB.	1st study (R)	5.98	3.54	70	159	0.90	4.5	16.4	98	113/69, 89	20/13, 16	—	3380	1910	44
		(E)	6.62	3.92	84	290	0.89	7.4	16.6	99	130/83, 101	32/17, 24	—	—	—	—
		21 months later (R)	4.98	2.96	58	136	0.92	4.6	17.6	94	102/64, 81	26/11, 16	4	3170	1835	47
	EH. MS. AI. NSR. IIC.	33 months (R)	5.00	2.98	57	131	0.86	4.4	16.9	95	116/67, 89	26/13, 19	—	3362	1785	47
		later (E)	7.32	4.36	75	366	0.90	8.4	17.8	98	121/70, 90	45/21, 34	—	—	—	—
		48 months (R)	4.88	2.90	58	119	0.86	4.1	16.7	94	115/68, 88	23/9, 16	—	3261	1952	41
		later (E)	6.67	3.97	87	326	0.95	8.2	17.6	95	138/78, 102	51/27, 39	—	—	—	—
#761. MD., F. 42 yrs.	EH. MS. AF. IIB.	1st study (R)	3.53	2.08	80	121	0.78	5.8	20.0	96	131/70, 94	30/17, 22	0	2525	1362	48
		(E)	4.28	2.52	110	292	0.83	11.6	20.5	99	120/84, 102	50/33, 41	3	—	—	—
#552. JS., M. 52 yrs.	EH. MS. AF. IIC.	1st study (R)	3.54	2.00	79	108	0.90	5.4	17.6	95	105/75, 89	28/12, 19	4	3310	1755	47
		2 weeks later (R)	4.15	2.33	60	128	0.84	5.5	17.4	98	123/71, 90	29/13, 19	5	3350	1880	44
		(E)	5.69	3.20	82	275	0.90	8.6	18.2	99	165/105, 130	49/25, 33	9	—	—	—
#555. EB., F. 29 yrs.	EH. MS. (T.I.) AF. Healed SBE. IIIC.	1st study (R) in CHF	2.64	1.42	91	122	0.98	8.6	16.2	96	104/70, 82	56/37, 44	11	4338	2402	44
		2 weeks later (R)	3.94	2.15	56	108	0.93	5.0	14.9	92	100/59, 81	40/16, 25	5	3750	2294	41

For abbreviations see end of table 1.
Healed SBE = healed subacute bacterial endocarditis.

nosed in the absence of left ventricular enlargement and a widened pulse pressure because pulmonary hypertension was either absent or only moderate at rest. The diagnosis of tricuspid insufficiency was made from right atrial pressure tracings in two patients (case 618, table 1; case 555, table 2) although the clinical evidence of the lesion was not present. This lesion is indicated in tables 1 and 2 by the bracketed letters T.I. None of the patients had any evidence whatsoever of an apical systolic murmur, nor did any have left ventricular enlargement by fluoroscopy or roentgenogram.

Prior to their evaluation by cardiac catheterization, all of these patients were closely observed in order to rule out, as far as possible, not only such complications as active rheumatic carditis, subacute bacterial endocarditis, and intractable heart failure, but also, to establish the best possible status obtainable by medical means. This period of observation in the hospital lasted two to three weeks in most instances.

After careful clinical appraisal of these individuals over a considerable period of time, physiologic studies were undertaken, using the method of cardiac catheterization as described in previous reports.[8-10] Observations were made at rest, during exercise, during acute digitalization and, in some subjects, before and after commissurotomy. The preoperative measurements were obtained shortly before surgery and in no instance was there thought to be any clinical change in the patient between the time of study and commissurotomy.

All of the eight subjects considered to have mitral block (table 1) were subjected to mitral commissurotomy. Two of the subjects with myocardial insufficiency also had mitral valvular surgery (table 2).

Interpretation of results. In order to determine the significance of any hemodynamic change produced in these subjects following acute digitalization or exercise, the criteria previously presented in detail have been employed.[8-10] To summarize these, any change in cardiac output greater than 9 per cent of the control value is considered significant, provided that in the studies made at rest, the oxygen consumption and the respiratory gas exchange ratio (respiratory quotient) do not vary by more than 18 cc. per square meter of body surface area, or 0.11, respectively. During exercise the measurement of cardiac output was considered valid only if respiratory gas exchange ratio was equal to or greater than the resting value, thus indicating that a steady state of exercise had been reached when the measurements involved in the Fick equation were made. As indicated in a previous communication,[9] a rough estimate of the normal response to the mild type of exercise employed in these subjects is at least a 650 cc. rise in blood flow per 100 cc. increase in oxygen consumption. Changes in lesser circulation blood pressures were considered significant only if they exceeded 5 mm. Hg, provided obviously that no change greater than this was noted during the control period in any individual patient. Since variations in heart rate are known to influence these pressures, especially in patients with mitral stenosis, particular care was taken to secure at least four control readings in order to obtain a good sampling. Although only one representative value is given in tables 1 and 2, the range of values can be seen in the illustrations where all pressure values are depicted.

A further word should be added here with regard to the interpretation of pressure tracings in patients with atrial fibrillation. With the marked variation in cycle length which may be encountered in this arrhythmia, there may be a greater variation in the amplitude of pulse waves than is found with a regular ventricular rate. For this reason in order to obtain representative pressure values, it is often necessary to analyse and average as many as 20 consecutive beats which may include three or four complete respiratory cycles instead of the usual two. This is true not only in single studies but is crucial when comparison of several separate studies is made.

The criteria which have just been reviewed are applicable to changes which may be encountered over a few hours' time. The magnitude of variations in pressure and blood flow which may occur in a normal individual in studies repeated at intervals of several months has not been determined and hence specific criteria for significant change are lacking. Recognizing the fact that long term variations are unknown, recourse was made to the only criteria available, namely, those previously described. One would appear justified in employing these since serial studies were also made each time in a steady, postabsorptive basal state as judged by oxygen consumption and respiratory gas exchange ratios. Although there may be changes in the patient's body weight between the several examinations, percentile changes in systemic blood flow have been calculated, using the cardiac indices.

Results

The 16 patients comprising this report have been divided into one group of eight (group I) in whom mechanical block at the mitral valve was considered the primary difficulty and a second group of eight (group II) in whom the clinical and physiologic findings suggest myocardial insufficiency as the predominant dysfunction. All 16 subjects had cardiovascular symptoms of varying severity. Indeed 12 of the 16 had had documented evidence of pulmonary or peripheral congestion at some time in their course. One particular historical feature differ-

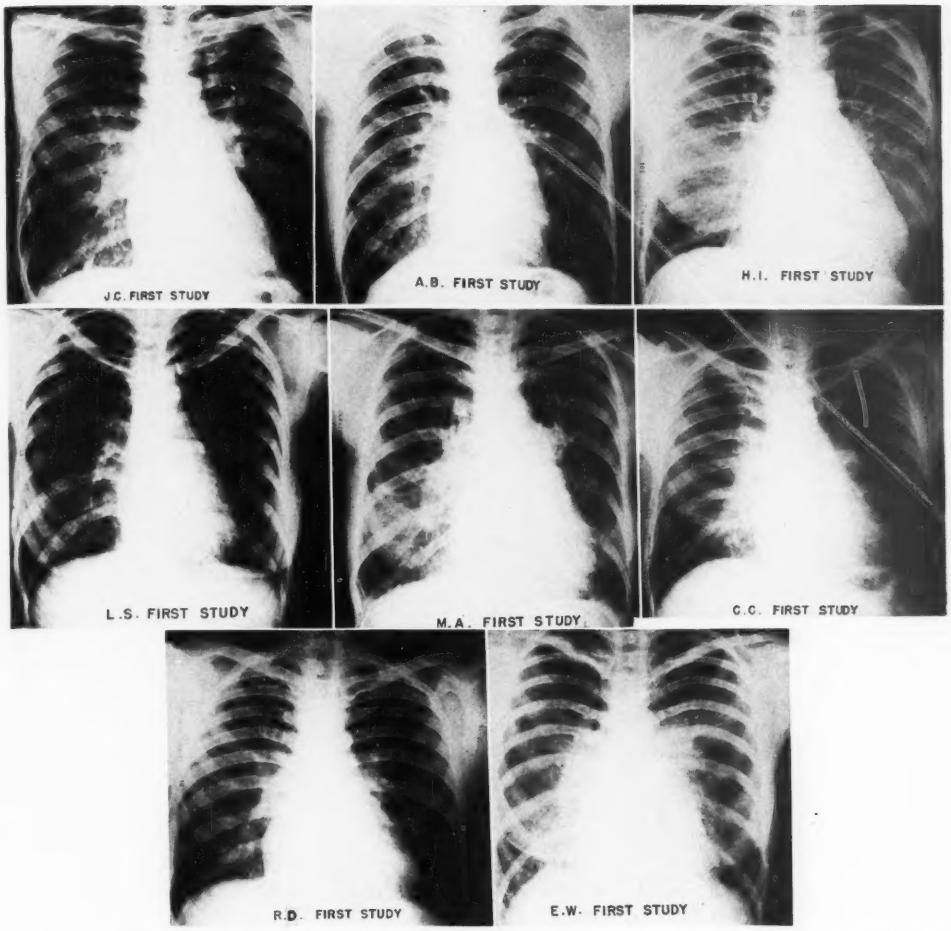


FIG. 1. Roentgenograms (posteroanterior 6-foot films) of patients in group I are in the same order as patients listed in table 1. J.C. = case 567, A.B. = case 595, H.I. = case 618, L.S. = case 663, M.A. = case 703, C.C. = case 707, R.D. = case 714, E.W. = case 713.

entiated one group from the other. Group I had almost constant and often progressive disability, group II, while completely incapacitated by their symptoms occasionally, nonetheless had relatively asymptomatic periods when they could resume their occupations. Comparison of other clinical features was less rewarding. The heart size, as shown in figures 1 and 2, was not always distinctive; although the largest hearts were found in group II, one can find hearts with slight to moderate enlargement in both groups. There were more patients with atrial fibrillation in group II, and none of these individuals showed the electrocardiographic pattern of right ventricular hypertrophy, although two (cases 699, 591, table 2) had a small double peak of R in V_1. On the other hand four patients in group I (cases 567, 703, 714, 713, table 1) showed an electrocardiographic pattern of right ventricular hypertrophy, as indicated by a large R wave and a late intrinsicoid deflection in the right precordial leads. Brief clinical summaries will be given together with the hemodynamic data of each of the subjects.

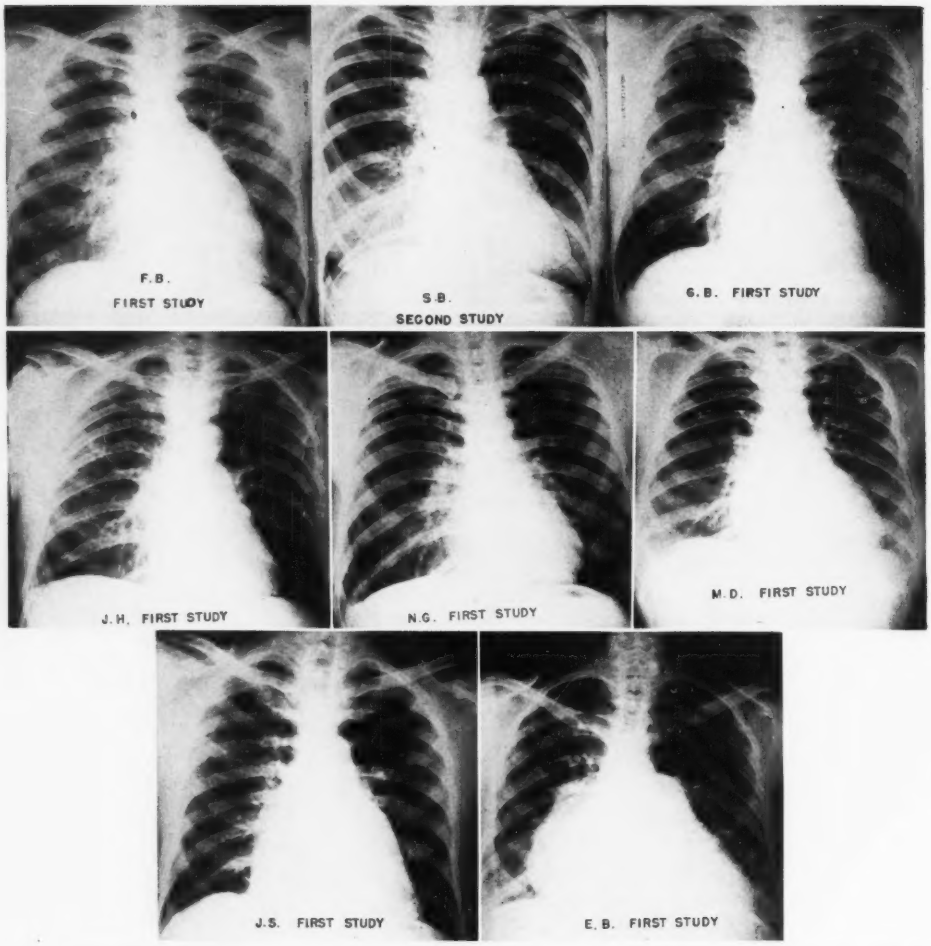


FIG. 2. Roentgenograms (posteroanterior 6-footfilms) of patients in group II are in the same order as patients listed in table 2. F.B. = case 699, S.B. = case 695, G.B. = case 635, J.H. = case 675, N.G. = case 591, M.D. = case 761, J.S. = case 552, E.B. = case 555.

Group I.—Mitral Block

In this group the hemodynamic findings were fairly uniform and support the concept that the major difficulty in circulatory function resulted from a mechanical block at the mitral valve which could be attacked surgically.

The first patient (case 567, table 1) had experienced exertional dyspnea for 12 years. For the year and a half prior to his first study, despite a more sedentary existence, dyspnea was present on the mildest exertion and orthopnea appeared. Small hemoptyses had occurred in the past three years. Digitalization and mercurial diuretics did not alter his symptoms although they rid him of mild edema. He was free of pulmonary rales and signs of peripheral congestion when first catheterized. His x-ray films, as well as those of each patient in group I appears in figure 1. Preoperatively a low cardiac output, severe pulmonary hypertension and a normal right ventricular diastolic pressure were present. The blood volume was slightly increased. As can be seen in figure 3, exercise produced an interesting combination of changes: a marked further rise in pulmonary hypertension with an insignificant rise in cardiac output (370 cc. increase in blood flow per 100 cc. increase in oxygen consumption). The right ventricular diastolic pressure reached abnormal levels during exertion. Commis-

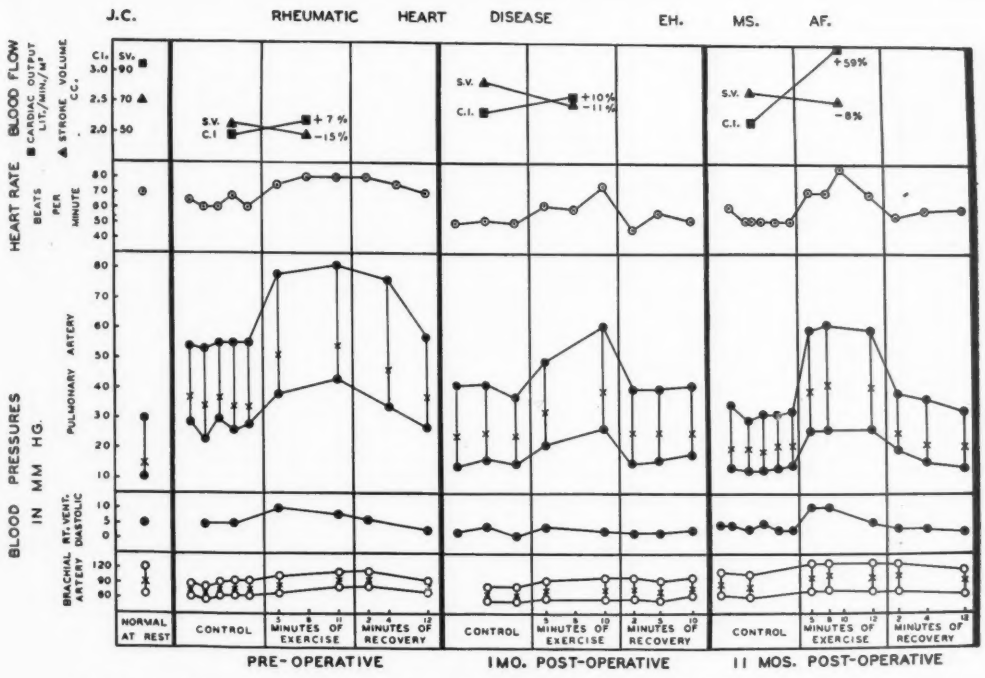


FIG. 3. Graphic representation of the hemodynamic findings in patient 567 (J. C.). For discussion see text. In this, and all subsequent figures, triangles = stroke volume; squares = cardiac index; target dots = heart rate; closed circles = pulmonary artery systolic and diastolic, and right ventricular end diastolic pressures; open circles = brachial artery systolic and diastolic pressures; cross marks = mean pressure. The normal values are plotted in the first vertical column.

surotomy effected a widening of the orifice as judged by the exploring finger and the postoperative course was not remarkable. One month later his clinical improvement was dramatic. He was comfortable on ward activity, orthopnea was absent and he was able to climb two flights of stairs without dyspnea. Maintenance Digoxin was continued in this interval, no changes in physical findings could be detected and the x-ray film of the heart had not altered appreciably. Postoperative studies at rest at this time (table 1 and fig. 3) demonstrated a fall of 15 mm. Hg in the pulmonary artery pressures. There was an increase in cardiac output (+21 per cent) and a fall in heart rate. The response to exercise differed from the preoperative study in that the entire level of pulmonary hypertension was lower and the right ventricular diastolic pressure did not rise above normal although the pulmonary blood flow was slightly larger than occurred on effort during the first study. The increase in blood flow of 434 cc. per 100 cc. of oxygen consumption, however, was not significantly different than preoperatively. After a period of convalescence, the patient returned to full time employment and remained asymptomatic. Maintenance Digoxin was continued. Physical examination, electrocardiograms and chest x-ray films were unchanged over the next 10 months. At the time of the third study, 11 months after operation, the most significant finding at rest was a further fall in pulmonary artery pulse pressure. On exertion the pulmonary artery pressures did not exceed those of the previous studies although the cardiac output, and hence the pulmonary blood flow, was considerably greater than had been encountered on previous studies, with a value of 635 cc. per 100 cc. increase in oxygen consumption. Right ventricular diastolic pressure rose on exertion. The brachial artery pressures were higher at rest and on exercise than preoperatively. There was little variation in blood volume throughout the whole period of observation. This patient is now over four and one-fourth years post commissurotomy and is fully employed.

The second patient in table 1, (case 595) had had two years of exertional dyspnea, cough and easy fatigue. During the month prior to admission he had several large hemoptyses associated with pulmonary edema and was by then dyspneic on slightest activity despite digitalis and mercurial diuretics. In the preoperative study, as seen in table 1 and figure 4, he had moderate pulmonary

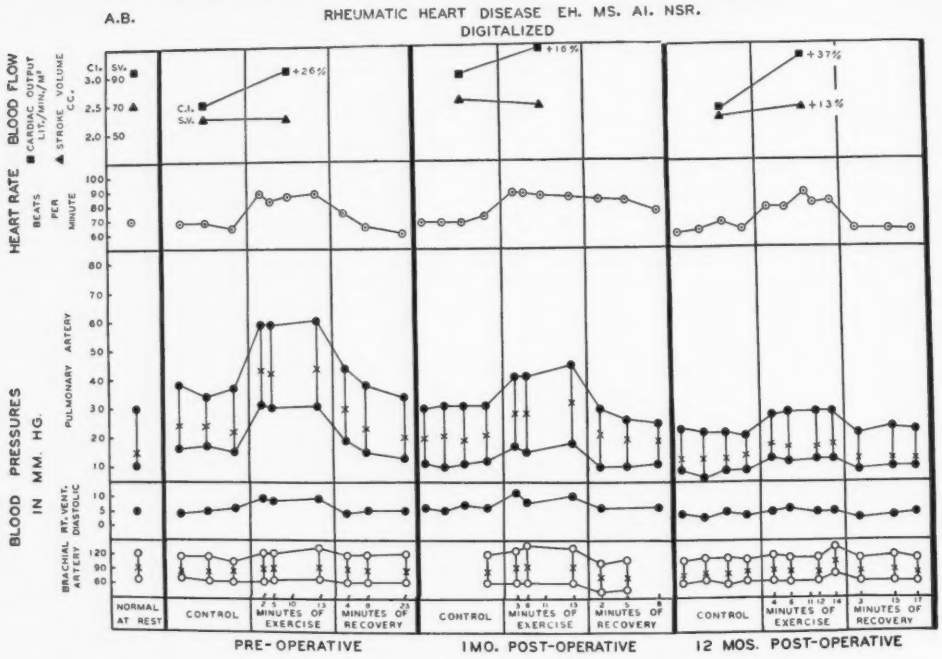


FIG. 4. Graphic representation of the hemodynamic findings in patient 595 (A. B.). For discussion see text.

hypertension and a low cardiac output at rest. Exertion called forth severe pulmonary hypertension and a high ventricular diastolic pressure with what was probably a normal increase in blood flow (658 cc. per 100 cc. increase in oxygen consumption) although the level reached was probably not normal. At operation the anterolateral commissure of the mitral valve was split by the finger. He was asymptomatic on ward activity but his physical signs, chest x-ray film and electrocardiogram were not altered at the time of the second cardiac catheterization, which was done one month postoperatively. Despite a larger systemic and pulmonary blood flow, the pulmonary artery pressures both at rest and during exercise were lower than preoperatively. The right ventricular diastolic still rose to abnormal levels on exercise. This patient was able to resume full activity, return to work and was asymptomatic at the time of the third study. This was performed 12 months after operation and the level of cardiac output at rest and during exercise remained essentially the same as was found preoperatively with a 500 cc. increase in blood flow per 100 cc. increase in oxygen consumption. However, he now had normal pulmonary artery pressures both at rest and during exercise. The ventricular diastolic pressure no longer increased abnormally during effort. Blood volume did not vary appreciably throughout the observation period. It is now four years since surgery and the patient no longer receives Digoxin.

The third patient (case 618, table 1) had 12 years of dyspnea and orthopnea for which she had been digitalized. In contrast to the previous patients, she had also had a large pulmonary infarction and cerebral emboli, three and two years ago. At the time of the first study exertional dyspnea and hepatomegaly were the chief clinical findings and physiologic measurements demonstrated a slightly reduced cardiac output, severe pulmonary hypertension and an elevated right ventricular diastolic pressure and blood volume. Pressure tracings in the right atrium were characteristic of tricuspid insufficiency. One month after commissurotomy, the patient had no dyspnea on ward activity. Hepatomegaly persisted and the other physical findings, the cardiac silhouette by roentgenogram and the electrocardiogram were the same as preoperatively. The significant hemodynamic changes at this time consisted of some reduction in pulmonary hypertension and blood volume, while the cardiac output and the end diastolic pressure in the right ventricle as read from the right atrial tracing, were not appreciably altered. Evidence of tricuspid insufficiency persisted in the right atrial tracings. Three and a

third years have elapsed since surgery and she is free of cardiac symptoms. She is unemployed for psychiatric reasons.

The fourth patient (case 663) of this group, a nurse and a diabetic, had known mitral stenosis for 10 years but was asymptomatic until she developed pulmonary edema two years before admission. Symptoms of pulmonary congestion grew progressively worse, forcing her to cease work. Digitalis, mercurial diuretics and rest did not bring appreciable symptomatic relief. She was, however, free of rales, hepatomegaly and edema when first studied. The preoperative measurements (table 1) revealed a normal cardiac output, blood volume and right ventricular diastolic pressure at rest, and moderate pulmonary artery hypertension. She had a bout of atrial flutter postoperatively which yielded to drug therapy. The physiologic measurements made one month after commissurotomy are not comparable to the preoperative values as the patient had considerable anxiety as can be seen by the elevated resting oxygen consumption (table 1). In view of this fact it is not clear whether in addition pressure values are comparable or not. Following operation she continued taking digitalis, but did not require diuretics. She returned to work in a busy premature infant unit after six months, and had no symptoms at all on any ordinary activities, but on one occasion did become severely dyspneic and noted blood streaked sputum while pulling oxygen tanks along the ward. The study made one year postoperatively showed a fall in pulmonary artery pressure at rest and no change in cardiac output or blood volume. On exercise these pulmonary artery pressures rose and the blood flow did not increase. It is now two and three-quarter years since operation and she has been free of cardiac symptoms, although her diabetes has been difficult to control.

The fifth subject (case 703), a concert pianist, sought relief of her symptoms by surgical means because, after seven years of increasing dyspnea which did not yield to digitalis and diuretics, she found herself unable even to play the piano without discomfort. Ankle edema was occasionally present. Free of physical signs of congestion when catheterized, she was found to have very severe pulmonary hypertension, increased blood volume and arterial blood oxygen unsaturation, the latter suggesting some fluid or other barrier to gas exchange (table 1). For technical reasons adequate data for calculation of cardiac output were not obtained. Her postoperative course was complicated by two episodes of paroxysmal atrial fibrillation which reverted to a normal sinus rhythm with quinidine. Six months postoperatively she was living a normal existence without any symptoms and required no digitalis. Cardiac catheterization at this time showed a fall of 13 mm. Hg in pulmonary artery mean pressure, a reduction in blood volume and return to a normal arterial oxygen saturation. The cardiac output was less than normal. In the two years following operation her marked clinical improvement has been maintained, permitting full-time work.

The sixth patient (case 707), a salesman, had been forced to a desk job by fatigue and exertional dyspnea increasing over a five-year period. Two years prior to admission he was in bed for five months with acute rheumatic fever. Four months before the catheterization studies he had a series of multiple systemic emboli—to brain, abdominal organs and arteries of the lower extremities. He had not been digitalized when first studied (table 1, fig. 5) and had no rales or evidence of peripheral congestion. Acute digitalization produced no alteration in the reduced cardiac output or the normal right ventricular diastolic pressure (fig. 5). There was no significant change in the level of the markedly elevated pulmonary artery diastolic and mean pressures but the systolic pressure did fall from 77 to 69 mm. Hg during the 40 minutes of study together with a slowing in heart rate. Although it was felt that this decrease in systolic pressure was due to reduction in heart rate, a second preoperative study was made after two weeks of maintenance Digoxin, in order to learn if there was any further diminution in pulmonary artery pressures after full digitalization. The clinical status remained the same and the study demonstrated that there was no further significant change in cardiac output and right heart pressures. No element of left heart failure then was apparent and hence the medication was withdrawn. The abnormal response to exercise during this second study was similar to that seen in the first patient, namely, an almost fixed cardiac output (with a blood flow increase of 206 cc. per 100 cc. increase in oxygen consumption) and the further aggravation of pulmonary hypertension with evidence of strain in right ventricular performance as manifested by a marked elevation of end diastolic pressure.[9] Operation was carried out in this patient and at one month postoperatively he was strikingly improved despite a lack of change in physical signs, heart size or electrocardiogram. Physiologic studies at this time (fig. 5) revealed a marked fall in pulmonary artery pressures at rest with only a small rise during exercise. The cardiac output which at rest was the same as preoperatively now increased satisfactorily during exercise (938 cc. per 100 cc. increase in oxygen consumption). There was really no change in plasma volume in this patient, although the red cell mass and hemoglobin were higher postoperatively. It is now 20 months since operation and the patient no longer has any disability and has returned to full activity, including some sports.

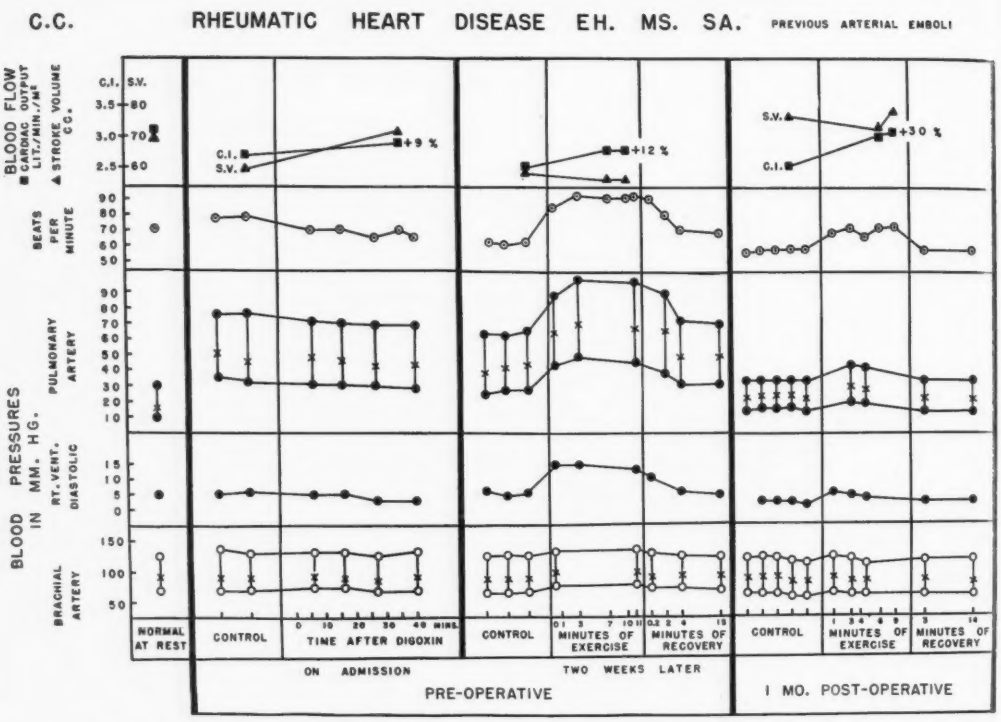


FIG. 5. Graphic representation of the hemodynamic findings in patient 707 (C. C.). For discussion see text.

The seventh patient (case 714), a bank accountant, had had acute rheumatic fever at the age of 10 years. On somewhat curtailed activity he had remained asymptomatic until one year before admission when progressive dyspnea appeared. He had one attack of paroxysmal nocturnal dyspnea three months before entry, and when first seen he was almost too short of breath to speak. Cough and blood streaked sputum occasionally accompanied severe dyspnea. He was not on any cardiac medication when first evaluated. As can be seen in figure 6, acute digitalization produced a reduction in heart rate accompanied by a slight decrease in the markedly elevated pulmonary artery pressures, but the low cardiac output fell slightly (−11 per cent) indicating the absence of heart failure, at least at rest, since other studies[11] have indicated that in the presence of failure Digoxin always calls forth an increase in cardiac output. The response to exercise was observed during the same catheterization study, and the leg motion was begun one hour after digitalization. The cardiac output rose subnormally (410 cc. rise in blood flow per 100 cc. of increase in oxygen consumption). A marked increase in heart rate and in all lesser circulation pressures were other features noted in the exertion period. No further digitalis was given. The patient was operated upon and six weeks later had noted considerable improvement. The cardiac output at rest was now 42 per cent higher than preoperatively and there had been a sharp fall in systolic pulmonary artery pressure with little change in the diastolic or mean. The response to exercise demonstrated even more clearly the improvement in function as the pulmonary artery pressures were not nearly so high despite the fact that the pulmonary blood flow was a liter greater than it had been during exercise in the preoperative study. However the blood flow increase per 100 cc. increase in oxygen consumption was still subnormal (513 cc.). The postoperative plasma volume was slightly increased over the normal preoperative value. At 19 months after surgery, his improvement continues despite increasing activity.

The eighth patient (case 713) was a 28 year old housewife whose cardiac history began five years before admission. At that time she had an hemoptysis in the sixth month of a second pregnancy. She was asymptomatic for a year after this until she had a pulmonary infarction immediately after delivery of her third child. Subsequently exertional dyspnea appeared and grew worse during the next

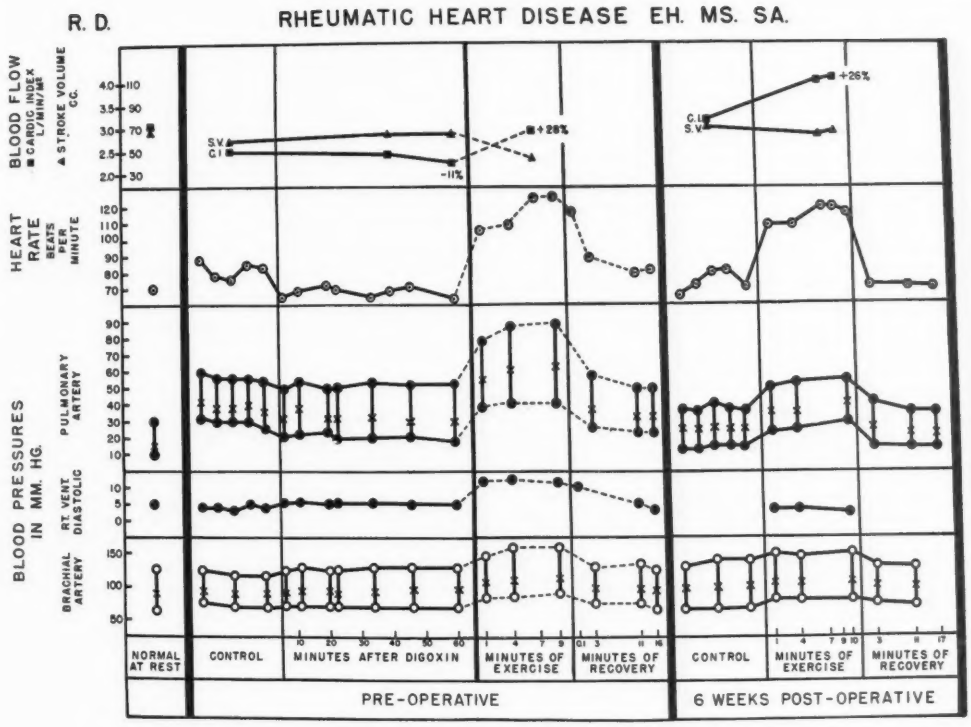


FIG. 6. Graphic representation of the hemodynamic findings in patient 714 (R. D.). For discussion see text.

three years. For the year prior to admission, because of this symptom, she was bed ridden either at home or in the hospital. A third pulmonary infarct precipitated mild right heart failure two months before admission. Digitalis had been tried on several occasions but since it never afforded her any relief of dyspnea, had been discontinued. Right heart failure had disappeared at the time of study. The values obtained at rest revealed severe pulmonary hypertension and a somewhat reduced cardiac output (table 1). Commissurotomy was performed and following a period of convalescence her functional capacity was strikingly improved. It is now 16 months since surgery and the patient is living a normal existence, having been able to resume care of her three small children as well as carry a full time job as a sales girl. She is asymptomatic without medication. This improvement was fully substantiated by the physiologic studies made at one year after commissurotomy. At this time pulmonary arterial and right ventricular pressures as well as the cardiac output were well within normal limits (table 1), the latter 35 per cent higher than before operation. On exercise the blood flow increased 790 cc. per 100 cc. increase in oxygen consumption which is a normal response and mild pulmonary hypertension appeared during the exertion. The plasma volume was normal and was less than preoperatively. The electrocardiographic changes were also quite striking as she no longer has evidence of a right hypertrophy pattern or of right axis deviation. There also has been a definite decrease in heart size.

In summary, all of these eight patients with mitral stenosis had a history of progressive cardiac disability and a disordered hemodynamic function characterized by moderate to severe pulmonary hypertension and either a low or normal cardiac output with a diminished blood flow response during leg exercise. At surgery the mitral orifice of each one was found to be narrowed, as judged by the fact that it would not admit the tip of the index finger. Following commissurotomy and widening of the orifice to a two-finger width, the pulmonary hypertension decreased to a greater or lesser degree both at rest and during exercise in every patient. This reduction was greatest in the systolic phase, hence producing

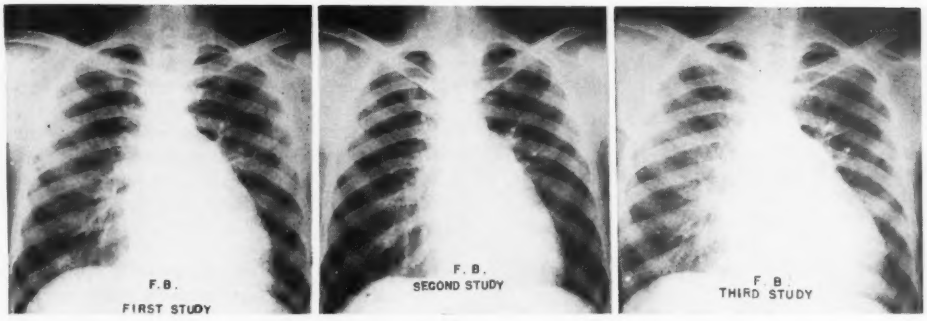
a fall in pulse pressure toward normal, despite the fact that in no instance was there a decrease in cardiac output or any significant difference in heart rate. In fact in three patients (cases 567, 714, 713) the blood flow was higher than preoperatively at rest and during exercise, while in a fourth (case 707), although the resting value after surgery was unchanged, it reached much higher values during exercise. This decrease in pulmonary artery pulse pressure suggests that blood has been mobilized out of this area postoperatively thus reducing the distention of the pulmonary vascular bed. Since left ventricular failure was excluded as far as possible by prolonged intensive medical therapy and specifically by acute digitalization studies in two patients, and since there was no striking or definitive reduction in total blood or plasma volumes in any subject after surgery, the reduction in pulmonary hypertension shown by this group of patients with mitral stenosis may be safely attributed to commissurotomy and was taken as evidence that mitral valvular block had been present and was at least partially relieved by surgery.

One point of interest should be stressed regarding the postoperative level of the pulmonary artery pressures. In only one of the eight subjects was this pressure restored to normal at rest and during exercise. One must assume that one of two causes, or both, is implicated in this residual hypertension, namely, the presence of some persistence of mitral block due to insufficient widening of the orifice by the surgeon, or due to pulmonary vascular atherosclerotic lesions. The behavior of these latter lesions, and indeed the contribution which they made in absolute terms to the level of pulmonary hypertension in any one patient, is not yet known. That the increased resistance due to these sclerotic lesions may be slowly reversible is suggested by the gradual decrease in pulmonary pressures over one year's time in one patient (case 595, table 1). However it could also be attributed to further mobilization of pulmonary blood volume. Thus it is conceivable that further improvement may occur in such individuals as time goes on, so long as there is no further mitral valve obstruction due to reactivation of the rheumatic valvulitis.

Group II.—Myocardial Insufficiency

In this group the hemodynamic findings at rest were uniform; during exercise, however, two patterns of response were found in the pulmonary circulation. After analysis these data support the concept that the major difficulty in these patients was not the result of mitral block, especially since valvulotomy proved ineffective in two instances, and could best be ascribed to imperfect myocardial function.

The first patient (case 699, table 2) in group II was a young handyman with a known heart murmur for nine years. His initial x-ray film, as well as those of each of the other patients in group II, appears in figure 2. He had his first cardiac symptoms, hemoptysis and cough, two years before the initial catheterization study. These symptoms cleared completely after digitalization and he returned to work, became relatively asymptomatic and hence eventually stopped taking the drug. Three months before study he again noted the onset of these first symptoms along with progressive dyspnea, and had severe right heart failure and atrial fibrillation. He was admitted to another hospital where digitalis again relieved the congestive failure and quinidine failed to revert the atrial fibrillation to sinus rhythm. Digitalis was continued after he was ambulatory and there were no signs of pulmonary or peripheral congestion when he was first evaluated. On this first catheterization the cardiac output was normal at rest, the pulmonary artery pressures were slightly increased with a greater rise in diastolic than systolic level, and the plasma volume was definitely elevated. On exercise the pulmonary hypertension increased somewhat. The mixed venous blood unfortunately clotted thus preventing the measurement of cardiac output during this exertion period. After two weeks of bedrest in the hospital a second catheterization was done. During this interval the only clinical change was a distinct decrease in heart size (fig. 7). On this second evaluation the cardiac output at rest was the same as on the first measurement; but, with the same ventricular rate, there had been a small but definite fall in the pulmonary artery pressures, a fall involving predominantly the diastolic and mean values, and the plasma volume had also decreased. Comparison of the resting hemodynamics in these two preoperative studies (table 2, fig. 8) reveals that the change on medical management is best explained as due to a decrease in left ventricular myocardial failure. This assumption is strengthened by the response to the exercise performance he made on this second study.



a b c

FIG. 7. Serial roentgenograms in patient 699 (F. B.). The posteroanterior 6-foot films were taken (a) at the time of the first, (b) the second and (c) the third cardiac catheterization. For discussion see text.

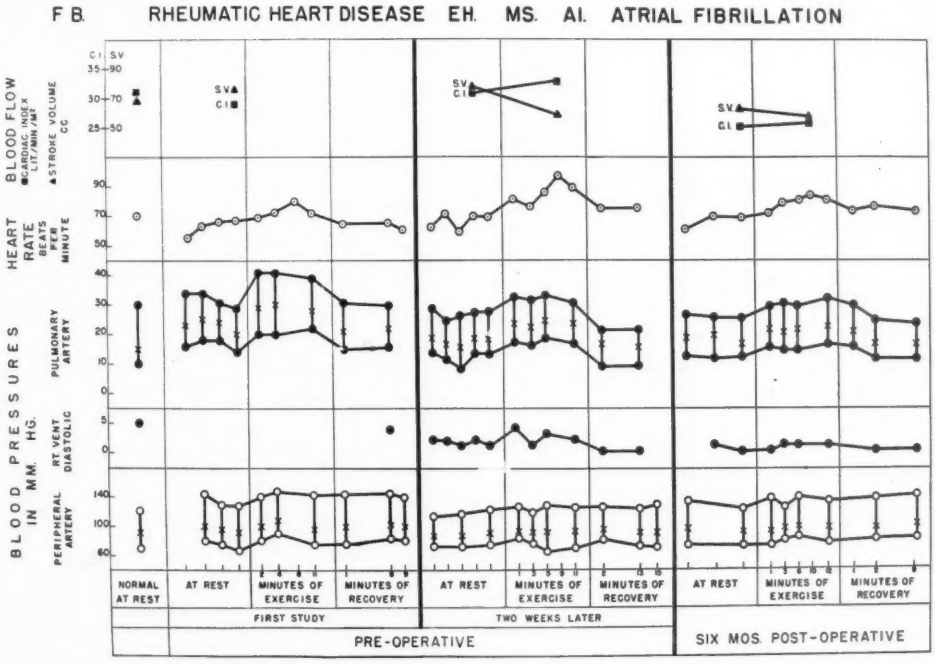


FIG. 8. Graphic representation of the hemodynamic findings in patient 699 (F. B.). For discussion see text.

Although the patient reached the same level of oxygen consumption during effort on both occasions, the second time, despite a ventricular rate which was even higher than in the first exercise period, there was no significant rise in pulmonary artery pressures as there had been when the mild left ventricular failure still existed. The cardiac output did not increase significantly on exercise (370 cc. per 100 cc. increase in oxygen consumption). It was recognized that this patient's resting hemodynamics and his response to exertion, namely, a fixed cardiac output without rise in pulmonary artery pressures, were quite different from those of patients in group I. The absence of significant pulmonary hypertension particularly was at variance with the usual experience in severe mitral valvular block. Since one could not, in view of our lack of knowledge, be certain if mitral stenosis in its mechanical aspects was responsible for the abortive response in cardiac output during exercise and in view of his history of

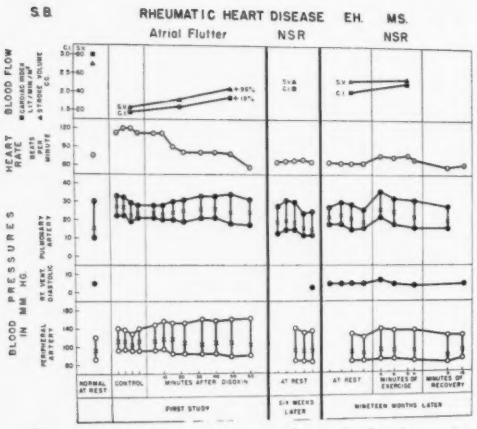


FIG. 9. Graphic representation of the hemodynamic findings in patient 695 (S.B.). For discussion see text.

repeated disability, this patient was permitted to undergo mitral commissurotomy. The orifice was somewhat narrowed and the edges split easily. For five months after operation, on limited activity he complained of little if any symptoms. Indeed he was in much the same state as preoperatively when he was out of congestive failure with a well-controlled ventricular rate. However, five months after surgery, following an upper respiratory infection, he once more went into congestive failure with increase in heart size, dyspnea, edema and hepatomegaly. After bed rest and diuretics the heart size again decreased but at the time of his third catheterization, when all signs of congestion had disappeared, it was still larger than preoperatively (fig. 7). At this time, six months postoperatively, (table 2, fig. 8) the cardiac output both at rest (−18 per cent) and during exercise was 1 liter lower than preoperatively, the blood flow was still fixed during exercise (196 cc. increase per 100 cc. rise in oxygen consumption), and the plasma volume was increased to the same level as before surgery. The pulmonary artery and right ventricular pressures were the same as on the second study, and were almost normal. They increased only very slightly if at all during exercise, as was the case during the second study. The operative intervention then had produced no improvement in hemodynamic function. Moreover, the level of blood flow was now below normal, probably as a result of the direct and continuing effects of the rheumatic process on the myocardium. It is concluded, therefore, that mitral block was not the primary cause of dysfunction in this man. It is now two years since commissurotomy, and the patient, remaining on digitalis, has not shown any clinical improvement. In fact, he has had to obtain lighter work than he was able to do preoperatively.

The second subject (case 695, table 2), a 44 year old woman, had been asymptomatic, save for an attack of rheumatic fever at the age of 16, until four weeks prior to study, when, following ingestion of a large amount of alcohol, she felt the sudden onset of a rapid heart beat. Subsequently, edema and severe right upper quadrant pain were noted. At the time of the first study she had signs of pulmonary congestion, a very large and tender liver, slight ankle edema and atrial flutter with 2:1 A-V response. Physiologically, the cardiac output at rest was quite low (fig. 9), there was moderate elevation of the pulmonary artery diastolic and mean pressures with only slight elevation in systolic and hence a small pulse pressure. The arterial blood showed oxygen unsaturation and the plasma volume was at the upper limits of normal. Acute digitalization with Digoxin produced a rise of 24 per cent in cardiac output and a slight decrease in pulmonary artery diastolic pressure. Following continued digitalization, mercurial diuretics and conversion to sinus rhythm by quinidine, she was recatheterized. At this time, six weeks after the first study, she had no clinical evidence of pulmonary or peripheral congestion, was in normal sinus rhythm and had received no quinidine for 18 days. The physiologic findings (table 2, fig. 9) indicated a resting cardiac output that was 41 per cent higher than the pre-Digoxin cardiac output and 13 per cent higher than the post-Digoxin figure. The pulmonary artery pressures were lower, particularly the diastolic level, and in fact were almost normal. The arterial blood oxygen was fully saturated and the plasma volume had fallen by nearly 300 cc. per square meter of body surface area. Comparison of these two evaluations suggests that congestive heart failure accounted for the findings of the first study, since the decrement in pulmonary artery pressures on the second study, despite a larger pulmonary blood flow, could only be explained as due to relief of left heart failure. On Digoxin she remained free of symptoms for 17 months, save for slight dyspnea on moderate to severe exertion. At this time a bout of flutter-fibrillation precipitated congestive heart failure and dyspnea at rest although she had continued to take Digoxin. Once again conversion to sinus mechanism was accomplished by quinidine and all signs of cardiac failure disappeared. At this time, 18 months after the first study (table 2, fig. 9), she was re-evaluated. Clinically and physiologically she was in the same state as at the time of the second study, with resting hemodynamics which were identical to those obtained at that time. When leg exercise was performed there was little or no rise in cardiac output (350 cc. per 100 cc. increase in oxygen consumption) and after a very slight initial increase at four minutes, there was no real change in pulmonary artery or right ventricular pressures. These hemodynamic observations are totally different from those of group I and hence it must be concluded that this

woman did not have an important degree of block at the mitral valve. In view of this, it is interesting to note that she had evidence of calcification of this valve by fluoroscopy.

The similarity of the hemodynamics at rest of the pulmonary circulation in these first two members of group II, both when they were in and then out of congestive failure, as well as during exercise, is striking. In view of the lack of improvement after commissurotomy shown by the first (case 699), the second patient was not offered surgery.

Just as these first two subjects in this group could be paired hemodynamically, so the next five patients were alike not only in their resting values but also in response to exercise which was characterized by an increase in pulmonary arterial pressure. They will be discussed individually and are well represented by the following case.

The third patient in group II (case 635, table 2), a 39 year old salesman, knew of cardiac enlargement and a heart murmur for 21 years, but had been asymptomatic until eight years before admission. Since then, easy fatigability was a prominent complaint along with dyspnea, intermittent ankle edema, orthopnea and one episode of hemoptysis despite digitalization. He was free of pulmonary rales, hepatomegaly and edema at his first catheterization. This latter (fig. 10) revealed a very low cardiac output at rest, minimal pulmonary hypertension with a normal right ventricular diastolic pressure and a plasma volume which was increased. On exercise, despite a subnormal rise in cardiac output (425 cc. per 100 cc. of oxygen consumption increase), pulmonary artery pressures were quickly increased to a moderately hypertensive level, in sharp contrast to the first two subjects in this group. This effort was accomplished without right ventricular strain as shown by the diastolic pressure remaining within normal limits. Although the resting pressure in the pulmonary artery was only slightly elevated, the exercise hypertension was disturbing, as it could be ascribed either to some degree of mitral block, which only became important when blood flow increased, or to left ventricular failure which appeared on exertion. Since his symptoms and exercise hypertension could be due to mitral block, commissurotomy was done and the surgeon widened a narrowed valve orifice which would not admit the tip of the index finger. Immediately postoperatively he was difficult to mobilize because of apprehension, hence any symptomatic change, if present, was impossible to appreciate. His physical findings, electrocardiogram and heart size did not alter. The postoperative catheterization at one month (table 2, fig. 10) showed no change over the preoperative performance at rest or during the same degree of exercise, except for some decrease in plasma volume. Three years and three months have passed since surgery and there is no evidence of clinical improvement.

The fourth patient (case 675, table 2), a 41 year old male, had no symptoms until the sudden onset of dyspnea associated with severe weakness, 10 days prior to hospitalization. He denied hemoptysis, chest pain and all other cardiac symptoms. He was in shock, had atrial fibrillation and was in acute respiratory distress on admission, with a liver which was considerably enlarged. The x-ray shadow indicated a large pulmonary infarct. Congestive failure yielded to digitalization and the wedge-shaped shadow in the x-ray film of the lungs disappeared in two weeks. He had been in the hospital nine weeks and free of signs or symptoms for seven weeks, when studied. The cardiac output and blood volume were normal and there was only a slight elevation of the diastolic and mean pulmonary artery pressures at rest with a systolic level within normal range. On exertion the blood flow increased subnormally (428 cc. per 100 cc. increase in oxygen consumption) and moderate pulmonary hypertension appeared without right ventricular strain. It was felt that the episode of failure in this man was associated with pulmonary infarction and the rapid ventricular rate and probably had little to do with significant block at the mitral valve since there was little or no resting pulmonary hypertension. It is possible that the hypertension during exercise resulted from persistent changes in the pulmonary vasculature consequent to the embolization and not from mitral disease.

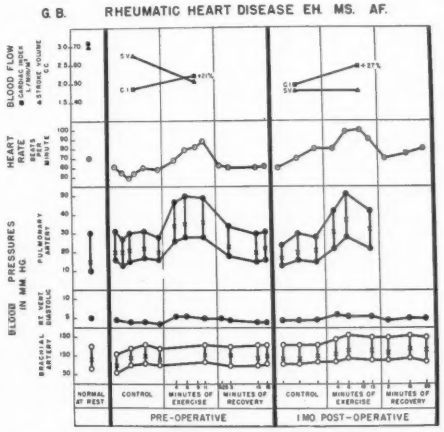


FIG. 10. Graphic representation of the hemodynamic findings in patient 635 (G.B.). For discussion see text.

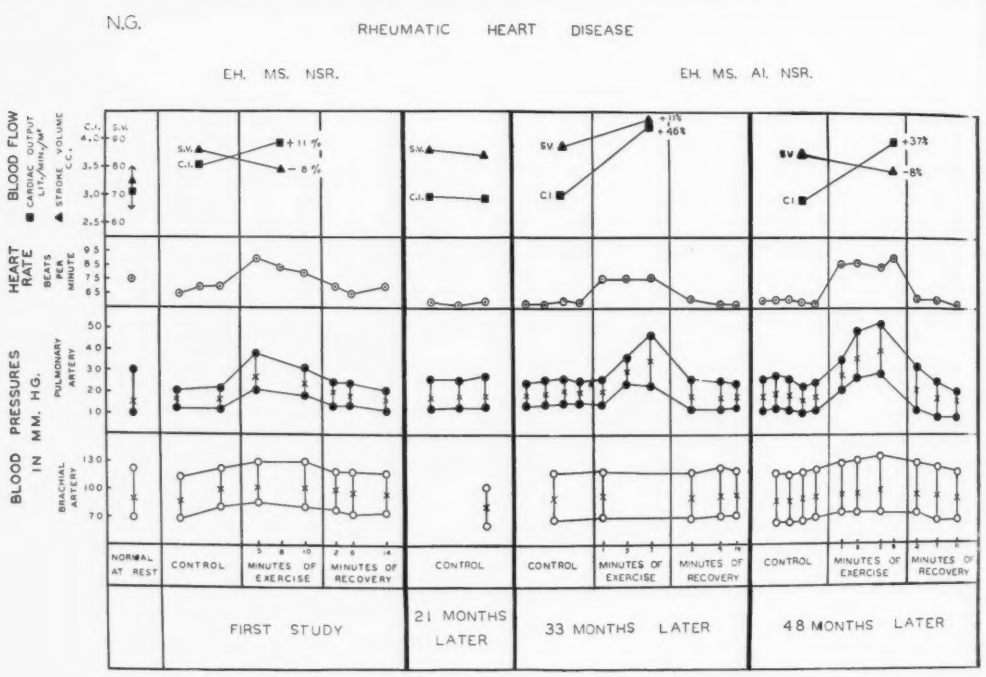


FIG. 11. Graphic representation of the hemodynamic findings in patient 591 (N. G.). For discussion see text.

The fifth patient (case 591, table 2) of this second group, whose first study was given in a previous report (9), had been a difficult problem to unravel. A 28 year old Puerto Rican laborer, he had had some mild exertional dyspnea for six months before a severe fist fight precipitated pulmonary edema and hemoptysis. After three weeks of bedrest he had no abnormal clinical signs save his murmur. His first catheterization (table 2, fig. 11) indicated a normal cardiac output, an increased plasma volume, and pulmonary artery pressures which were nearly normal at rest and which rose somewhat during exercise and then declined although exertion continued. This effort called forth an increase in blood flow of only 290 cc. per 100 cc. increase in oxygen consumption. This performance did not suggest the same hemodynamic state as was seen in the patients of group I, particularly since a fall in pulmonary pressures as exercise continued has never been seen in our experience in patients with mitral block if exercise remains steady.

The patient was lost to follow-up until 21 months after the first study, during which interval he was asymptomatic. Mild dyspnea had recently recurred and the question of mitral surgery was raised. A second evaluation (table 2, fig. 11) showed no change in resting hemodynamics. In view of these findings it was felt that surgery was not warranted. After another lapse of time, during which he worked as a dishwasher and peddler, mild dyspnea again brought the patient to the clinic. At this time a basal diastolic murmur could be heard in the fourth left intercostal space close to the sternum. A third catheterization, done 33 months after the first (table 2, fig. 11), again revealed no change in dynamics at rest. During exercise, which at this time was carried out at a higher level of oxygen consumption, the cardiac output rose 586 cc. per 100 cc. increase in oxygen consumption, a value which is lower than a normal individual would achieve. Pulmonary pressures again rose and this time remained elevated at a higher plateau during the whole of exercise. Complaints of mild dyspnea and easy fatigability continued for the ensuing 15 months. The liver became slightly enlarged, but was never tender. There were no other objective evidences of systemic or pulmonary congestion. Mercurial diuretics were reported to alleviate dyspnea but did not affect the size of the liver. The enlargement of the latter may well have been related to the patient's excessive alcoholic intake. At the time of the fourth study the heart was slightly larger than noted previously, but in other respect the clinical findings were the same as at the third study. Similarly the hemodynamic findings were unchanged. The appearance of the basal diastolic murmur and the enlarging heart

suggested that active rheumatic endocarditis and myocarditis were present. For this reason and because resting pulmonary artery pressures were unchanged for four years and because of the surgical experience of the third subject in the group (case 635), no operation was offered this man.

The sixth subject (case 761, table 2) had as her prime complaint palpitations when excited. She had chorea at age 14, and had led a very active life as a swimming instructor and clerk. Six years ago she had had some dizzy spells, was digitalized and told to curtail her activities. As a result of emphasis on her previously unknown heart lesion, the patient became increasingly apprehensive, conscious of palpitations but had no dyspnea. Her physician referred her to the hospital for evaluation in reference to surgery. There were no abnormal signs save the cardiac murmur and abnormal rhythm when she was studied. It was evident during the physiologic evaluation that she had a labile ventricular rate. When she had been at rest for sometime, however, her pulmonary artery pressures were only minimally elevated, blood volume was normal but the cardiac output was low. A subnormal rise in blood flow (257 cc. per 100 cc. increase in oxygen consumption) occasioned a brisk rise in pulmonary artery pressures and a slight fall in systemic artery pressures at a time when the ventricular rate reached 158. Surgery was not felt to be indicated in view of her resting pulmonary artery pressures.

The seventh patient (case 552, table 2), a 52 year old elevator operator, had had several attacks of rheumatic fever until the age of 30, but after digitalization for his first bout of failure at age 36, was able to work steadily until one month before admission, when, on losing his job, he stopped taking digitalis for financial reasons. Within a short while dyspnea, orthopnea and edema returned, and he was hospitalized. After bed rest, all signs of failure receded and the hemodynamics at rest were characterized by minimal pulmonary hypertension, a low cardiac output and an elevated plasma volume. The patient was digitalized and showed no rise in cardiac output in this acute study as described in a previous report.[11] On examination two weeks later there were no circulatory changes from the first catheterization, and, at this time, when the man exercised he developed pulmonary artery and right ventricular diastolic hypertension with a rise in cardiac output which, in the light of our recent experience, must be classed as subnormal (590 cc. per 100 cc. increase in oxygen consumption).

In summary, all of the subjects in group II had moderate to severe cardiac symptoms which were episodic in their occurrence. The last five patients presented (cases 635, 675, 561, 761, 552) all had minimal if any pulmonary hypertension at rest and a rise in these pressures during exercise, in contrast to the first pair of subjects in group II (cases 699, 695) whose resting pulmonary artery pressures were also almost normal but in whom these pressures did not increase significantly on effort. In each of these subgroupings one representative patient was subjected to mitral surgery as a pilot investigation. In neither one was there clinical or physiologic evidence of any improvement in hemodynamic function after commissurotomy. If one can accept the experience encountered in group I as characteristic of mitral block, a state which was expressed hemodynamically by pulmonary hypertension at rest which was aggravated by exertion, and which yielded to valve fracture as attested to not only by clinical improvement, but also by objective measurements of a decrease in lesser circuit pressures postoperatively, then the patients in this second group do not have appreciable mitral valve block. The subnormal response in cardiac output during exercise, be it normal or low at rest, was common to all of these patients and hence does not help in differentiating them.

If one does not accept the deranged dynamics in these individuals in group II as chiefly the result of mitral block, one must attempt a further explanation of their difficulties. All are victims of rheumatic heart disease and hence it is likely that myocardial lesions exist in them as well as valvular cicatrices. Although mitral valvular damage has occurred as indicated by auscultation, there appears to be little hemodynamic evidence of obstruction to blood flow at rest at the mitral valve in these patients with almost normal lesser circulation pressures. Furthermore in the two patients whose pressures were not increased with exercise, there seemed to be further proof of no impedance to blood leaving the left atrium. In none of these individuals, however, does the cardiac output respond normally to the demands of exertion. This suggests an insufficiency in myocardial performance which is not related to mechanical obstruction within the circulatory channels. Indeed, this insufficiency is probably the major circulatory defect of the patients in group II. In those five subjects in whom pulmonary

hypertension appeared on exertion this insufficiency had progressed to a further stage than in the first two subjects who remained normotensive, and one might even say they had reached the stage of frank left heart congestive failure on effort. In all instances save one (case 552) the effort, however, was not severe enough to produce physiologic evidence of right heart failure, namely, a rise in right ventricular diastolic pressure.

An example of a still more advanced phase of this type of predominantly myocardial insufficiency in a patient with rheumatic heart disease and mitral stenosis is presented in the *eighth patient* (case 555, table 2) of group II. Her first study was done while she was in right and left sided congestive failure and physiologically demonstrated severe pulmonary hypertension with a high right ventricular diastolic pressure, a low cardiac output and a very large blood volume. Two weeks later, after digitalization, mercurials and bedrest, a very striking decrease in right heart pressures had occurred in association with a rise in cardiac output. This case serves to demonstrate the point that pulmonary hypertension due predominantly to left heart failure exists in some patients with mitral stenosis, and that this hypertension declines in response to medical management. It may well be that after further treatment this patient would have presented the same hemodynamic picture at rest as demonstrated by the first seven patients in group II.

Discussion

It has long been an accepted clinical teaching that a block at the mitral valve would produce pulmonary hypertension either with or without anatomic changes in the pulmonary vascular bed. The physiologic resultants of this mechanical interference with flow from the left atrium were eventually established in absolute terms and in addition to confirming the presence of pulmonary hypertension, a low cardiac output was often seen. The latter was also ascribed, at least in part, to impedance to blood flow at the valve. Since mitral stenosis can progress to a stage of blocking egress of atrial blood and hence producing pulmonary hypertension, it is important to learn more about the various stages of mitral block. It has been shown that the mere ausculatory finding of the typical murmur, particularly in the absence of symptoms, does not imply elevation of pulmonary artery pressures. Indeed, there are patients with this murmur and perfectly normal cardiodynamics.[9, 12, 13] It is likely that there are various degrees of obstruction at the valve and that minor ones do not interfere with circulatory performance, at least at the levels of activity which have been measured so far. Perhaps severe taxing exertion may uncover such small obstructions. Once pulmonary hypertension exists at rest in a patient with mitral stenosis and rises with exercise, mitral block can be assumed to have become important. It is recognized, of course, that left ventricular failure can and often does produce pulmonary hypertension independently of any valvular lesion, and this cause for pulmonary hypertension should be ruled out, whenever possible, in the course of evaluating the dynamics of mitral stenosis.

If then, failure of the left heart can be excluded in a patient with mitral stenosis and pulmonary hypertension, it would appear that mitral block exists. The subjects in group I were characterized by this hypertensive dynamic state and were partially relieved of it by surgery as evidenced by the disappearance or decrease in elevated pulmonary artery pressures. Since both symptoms and pulmonary hypertension were ameliorated by surgical dilatation of the valve orifice, it would seem that significant mitral block produces pulmonary hypertension at rest, and, without this hypertension at rest, significant mitral obstruction does not exist. The poor operative result in the second group of patients lends strength to this conclusion.

Furthermore, the totally different dynamics in this second group, namely, absence of pulmonary hypertension but a restricted cardiac output, have pointed out a physiologic state which is certainly abnormal, but which probably springs from intrinsic myocardial insufficiency and not from mechanical cause. It is suggested that the pulmonary hypertension which some of these subjects demonstrate

during exercise is a reflection of this poor myocardial function in that it implies left heart failure during stress, a response which the authors have found in patients with non-valvular cardiac disease.[14] This point is illustrated in figure 12 which depicts the findings at rest and during exercise in a 42 year old woman with hypertensive cardiovascular disease and cardiac enlargement without cardiac symptoms. These observations were made before and three and one-half weeks after digitalization. At rest she had mild pulmonary hypertension with a normal cardiac output and right ventricular diastolic pressure. During exertion there was an inadequate rise in cardiac output and she developed severe pulmonary hypertension. The second study, made when she was fully digitalized, demonstrated no change at rest or during exercise when compared with the findings of the first study. These data indicate that even in the absence of the clinical expressions of left ventricular failure, the hemodynamic state of this patient demonstrated a type of insufficiency of the left ventricular myocardium which persisted in spite of digitalization.

The question could be raised of course, are not all these patients in group II merely examples of a mild degree of stenosis at the valve? In the first two subjects of this group it is impossible to imagine any real valve obstruction in the absence of pulmonary hypertension either at rest or on exertion. Insofar as the five patients who developed pulmonary hypertension only on exercise are concerned, it is difficult to accept such an explanation since it would imply less disability on the part of these subjects than those in group I, and yet, from a clinical point of view, their hearts are as large or larger, there is a higher incidence of atrial fibrillation and the same or greater number of bouts of congestive failure; in summary, they show as much or more clinical disability as the patients in group I with block. Moreover in the two patients of group II in whom the valve was widened by surgery, there was no physiologic or clinical amelioration. A review of those previous reports which give sufficient detail to permit analysis of data indicates that there

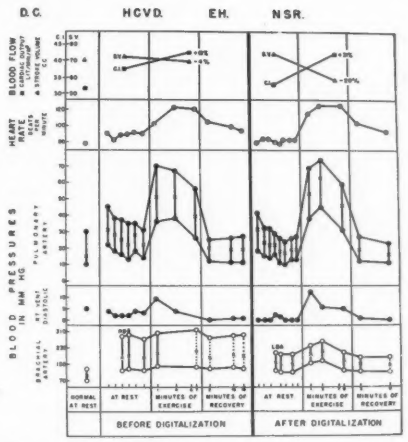


FIG. 12. Graphic representation of the hemodynamic findings in patient 778 (D.C.). For discussion see text. The dotted lines indicate the appearance of pulsus alternans in the brachial artery. There was no real change in brachial artery systolic pressure between studies, as a discrepancy in this pressure was always found between the right and left brachial arteries.

is no unequivocal improvement in hemodynamics after surgery in subjects with little or no resting pulmonary hypertension,[4, 13] which lends support to the concept that in the absence of resting pulmonary hypertension, significant mitral block does not exist.

It is evident then that there exists in some patients with symptomatic rheumatic mitral stenosis, a hemodynamic state which, in the absence of outspoken left heart failure, is characterized by little or no pulmonary hypertension and yet is associated with an abnormally low response in cardiac output on exertion. More than half this group of eight had low outputs at rest and one wonders, in view of this fact, whether the level of blood flow in patients with mitral stenosis, at rest and during exercise, is not chiefly an index of myocardial integrity and is much less influenced by the mechanical valvular block than was formerly postulated. In support of this suggestion one notes that only three of the eight patients with successful commissurotomies (group I) had any change in the resting level of cardiac output after surgery.

The importance of differentiating the group with mitral block from that with predomi-

nantly myocardial insufficiency—and the catheterization data appear to make this a feasible differentiation—is obvious when one considers offering surgery to any patient with mitral stenosis. It would seem only logical to insist on a demonstration of pulmonary hypertension in each prospective candidate in order to avoid selecting one with predominantly myocardial insufficiency. It should be recalled that such patients are not rare since this group of eight was culled out of a total of 45 patients with mitral stenosis who were studied physiologically as possible candidates for mitral surgery.

The abnormal dynamic state which is considered to have as its basic mechanism poor myocardial function, is not to be confused with the state of certain other patients with mitral stenosis who also do not have pulmonary artery hypertension. These latter subjects are either asymptomatic entirely or have symptoms which are noncardiac and often are iatrogenic. Studies in these individuals have revealed a normal level of cardiac output and a normal response of this function on exertion.[6, 9, 13]

The 16 patients discussed in this presentation were selectively chosen and separated into two groups because of the predominance of one or the other basic dysfunction, namely, mechanical obstruction or myocardial insufficiency. It is recognized that in any one individual with rheumatic heart disease there may well be an element of both present, making analysis difficult. Unfortunately there is no way of defining the exact etiology of the limitation of myocardial function in the second group. Rheumatic carditis is certainly likely; but whether this is in the active stage or not cannot be stated. The data demonstrate that this hypodynamic state exists in patients with mitral stenosis who have no evidence of mechanical valve obstruction.

From the data presented in this paper, one can conclude that without proven pulmonary hypertension of moderate to severe degree at rest there is probably little or no important degree of block at the mitral valve. Furthermore, patients with mitral stenosis and little or no hypertension must be carefully and extensively evaluated. In the light of our current knowledge they should not, at least for the present, be subjected to commissurotomy since they may be suffering either from predominantly myocardial insufficiency, a stage herein described, or have no circulatory dysfunction at all.

Summary and Conclusions

1. Sixteen patients with rheumatic heart disease and pure mitral stenosis who were studied by the cardiac catheterization technic, were selected to demonstrate the relative importance of mitral block and myocardial insufficiency in this disease.

2. Analysis of the dynamics at rest and during exercise has permitted a division of these patients with mitral stenosis into two groups, one with mitral block characterized by pulmonary hypertension of varying degrees and a fixed or subnormal response in cardiac output on exercise, and the other in whom little or no pulmonary hypertension exists but in whom cardiac output does not increase normally on exercise. In the latter group myocardial insufficiency was felt to be the predominant lesion uncomplicated by any important element of mechanical block.

3. The importance of recognizing the existence of a group of rheumatic patients with mitral stenosis and primarily myocardial insufficiency is emphasized since commissurotomy will not produce any improvement in function in such cases.

Summario e Conclusiones in Interlingua

1. 16 patientes con cardiopathia rheumatic e pur stenosis mitral, qui esseva studiate per medio del technica de catheterisation cardiac, esseva seligite pro demonstrar le importantia comparative de bloco mitral e insufficientia myocardiac in iste morbo.

2. Super le base del dynamica a reposo e a exercitio il esseva possibile gruppar iste patientes con stenosis mitral in duo categorias: le prime con bloco mitral characterisate per hypertension pulmonar de varie grados e un fixe o subnormal responsa de rendimento cardiac in observationes a exercitio, e le secunde in qui pauc o nulle hypertension pulmonar existe sed in qui le rendimento cardiac

non monstra le normal augmento post exercitio. In le secunde gruppo nos supponeva que insufficientia myocardiac esseva le lesion predominante, non complicate per ulle importante elemento de bloco mechanic.

3. Le importantia de recognoscer le existentia de un gruppo de patientes rheumatic con stenosis mitral e un insufficientia primarimente myocardiac es sublineate proque in tal casos nulle melioration functional pote esser attingite per medio de commissurotomia.

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The Diagnosis of Tricuspid Insufficiency

Clinical Features in 60 Cases with Associated Mitral Valve Disease

By GONZALO SEPULVEDA, M.D. AND DANIEL S. LUKAS, M.D.

In a series of 146 patients with mitral stenosis studied by cardiac catheterization, 60 were found to have right atrial pressure curves diagnostic of tricuspid insufficiency. The clinical and hemodynamic features of these patients are reviewed. The oft-cited, classic manifestations of tricuspid insufficiency were found with relative infrequency and the diagnosis had been made clinically in less than one fourth of the cases. Modification of criteria for the diagnosis of tricuspid insufficiency is suggested.

INSUFFICIENCY of the tricuspid valve (T.I.) produces characteristic alterations in the right atrial and peripheral venous pressure curves.[1-3] The essential component of these alterations is an increase in pressure during ventricular systole. Clinical diagnosis of the lesion has been dependent on recognition of this systolic pulsation in the systemic veins, chiefly those of the neck and liver.

The right atrial pressure curve that was originally described by Bloomfield and associates[3] as diagnostic of tricuspid insufficiency has been found with surprising frequency among patients with advanced mitral disease.[4-6] Failure to recognize the tricuspid lesion clinically in a very large proportion of the cases suggested that the present diagnostic criteria may be too stringent. Accordingly, with the purpose of identifying the most common manifestations of tricuspid insufficiency, a review was made of the clinical features of 60 patients with chronic rheumatic heart disease and predominant mitral valvular involvement in whom associated tricuspid insufficiency was demonstrated by cardiac catheterization. In addition the hemodynamic data obtained in these patients was analyzed and compared with those from a group of patients without tricuspid insufficiency but with a similar degree of mitral involvement.

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This study was aided by a grant from the New York Hospital-Cornell Medical Center Research Fund.

Presented in part at the Second World Congress of Cardiology and Scientific Sessions of the 27th Annual Meeting of the American Heart Association, Washington, D. C., September 12–17, 1954.

Dr. Sepulveda is a Fellow of the Rockefeller Foundation from the University of Chile.

MATERIAL AND METHODS

The material for this study consisted of 60 patients with chronic rheumatic heart disease and moderate to severe mitral stenosis. Almost all were undergoing evaluation for mitral valvuloplasty. Some degree of mitral insufficiency was present in 41 and at valvuloplasty was usually estimated to be mild. Ten patients had an associated aortic lesion. The average age was 40.6 years (range, 21 to 60). The 40 females had an average age of 41.9 years (range, 24 to 60); the 20 males, 38 years (range, 21 to 52).

In the analysis of the clinical features particular attention was paid to the following criteria listed by The Criteria Committee of the New York Heart Association as diagnostic of tricuspid valve disease[7]: cyanosis, often combined with icterus; distended neck veins, which may show unusually marked pulsations; rare orthopnea; frequent auricular fibrillation; enlarged liver, which may show unusually marked pulsations; recurrent ascites; enlargement of the right atrium and clear lung fields at the roentgenologic examination; right axis deviation of QRS in the electrocardiogram. Particularly suggestive of tricuspid insufficiency are: systolic pulsation of the cervical veins and often of the veins of the extremities and systolic expansile pulsation of the liver. The Committee states: "The clinical diagnosis of tricuspid valve deformity, although difficult, can be made correctly in an appreciable number of instances. It should not be made in the presence of congestive failure, since then tricuspid incompetency is frequently present. It should be suspected in a rheumatic patient with mitral stenosis who has persistently enlarged liver, engorged neck veins and recurrent ascites, but who is free of orthopnea. Murmurs rarely contribute to the diag-

nosis of this valvular deformity since it is difficult or impossible to distinguish them from the murmurs of mitral stenosis and insufficiency which are almost invariably present in these patients."

The clinical signs reported herein were observed during hospitalization of each patient for cardiac catheterization. All patients were receiving digitalis; those who had cardiac failure were under as optimum medical control as was deemed possible at time of catheterization.

Conventional roentgenograms of the chest, available in 59 cases, were examined with regard to overall cardiac size, right atrial enlargement and pulmonary vascular congestion. An estimate of the degree of enlargement of the right atrium was based on the distance the atrial border protruded to the right from the midline of the thorax in the posteroanterior roentgenogram. The distance was 4 cm. or less for slightly enlarged atria, 4 to 6 cm. for moderate enlargement, 6 to 8 cm. for severe enlargement and over 8 cm. for giant-sized atria. These measurements were selected after review of 24 available angiocardiograms which provided an accurate delineation of the right atrium.

Cardiac catheterization, recording of pressures and determination of cardiac output were performed by methods previously described.[4, 5] Exercise was performed with the patient in the recumbent position and consisted of flexion and extension of the legs at the rate of one cycle per two seconds for five minutes. All right atrial pressure tracings were carefully examined; only those with an unequivocal pattern of tricuspid insufficiency were included. An associated tricuspid stenosis was ruled out by comparing the Z point[8] (point on the right atrial curve that corresponds in time to the onset of ventricular systole) with the right ventricular end-diastolic pressure[9] and by comparing the mean right atrial pressure during ventricular diastole to the mean right ventricular diastolic pressure. Two patients with a mean pressure gradient greater than 2 mm. Hg (6 mm. in one and 17 mm. in the other) from right atrium to right ventricle during diastole were not included because of this evidence of tricuspid stenosis. Both tricuspid and mitral stenoses of one patient were treated surgically.

Results

Clinical Features (fig. 1)

Chronic Auricular Fibrillation. Fibrillation of 6 months to 15 years duration was present in 58 (96.7 per cent) of the 60 patients. Two had normal sinus rhythm. Of 146 patients with rheumatic mitral lesions studied in this laboratory, the incidence of tricuspid insufficiency in those with atrial fibrillation was considerably and very significantly greater ($p < 0.01$) than in those with normal sinus rhythm (fig. 2).

Enlargement and Pulsation of the Liver. Hepatomegaly that persisted in spite of the absence of peripheral edema or attainment of "dry weight" by salt restriction and mercurial diuretics was found in 53 (88.3 per cent) of the patients. Definite systolic pulsation of the liver was present in only nine (15 per cent). In more than two-thirds of those with hepatomegaly the liver edge was more than two finger-breadths below the right costal margin in the midclavicular line.

Right-sided Failure, as manifested by the chronic need for mercurial diuretics to control peripheral edema, was present in 41 (68.3 per cent) patients. It was considered severe (two or more mercurial injections per week) in 21

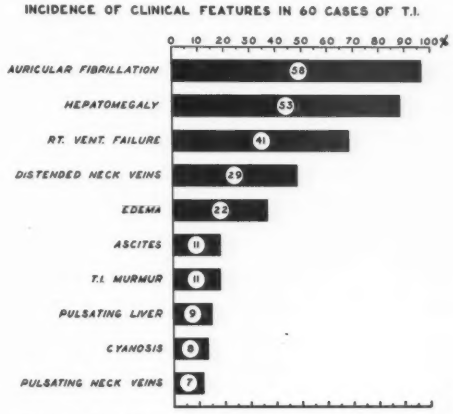

FIG. 1. Incidence of clinical features in 60 cases of tricuspid insufficiency. Scale in per cent. Number of cases is encircled.

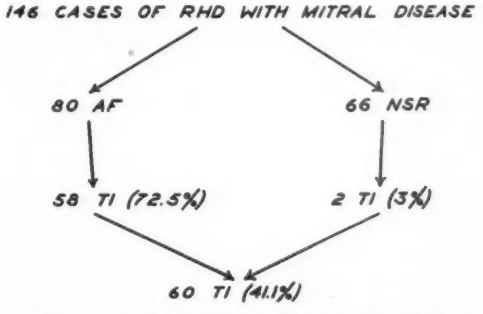

FIG. 2. The incidence of auricular fibrillation (A.F.) and normal sinus rhythm (N.S.R.) and tricuspid insufficiency (T.I.) among 146 cases of rheumatic mitral disease.

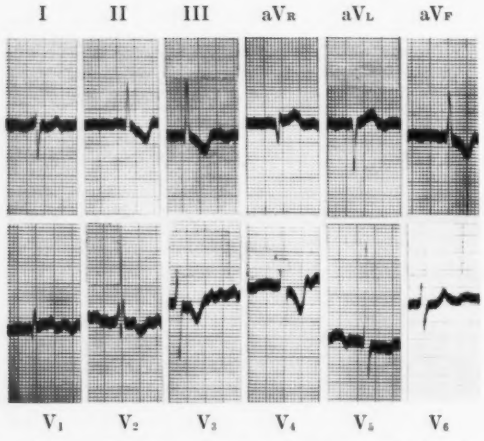

FIG. 3. Electrocardiogram of a 32 year-old female with severe mitral stenosis and tricuspid insufficiency, hepatomegaly and pulsations of neck veins. Note small amplitude, late onset of intrinsicoid deflection and rsR′ configuration of QRS in V_1 and the deep S waves in the other V leads. An rsR′ pattern is prominent in V_2.

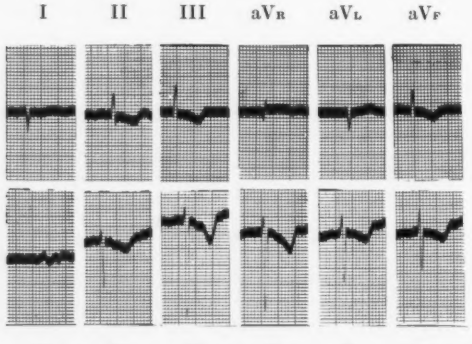

FIG. 4. Electrocardiogram of a 43 year-old female with advanced mitral disease, tricuspid insufficiency, hepatomegaly, marked orthopnea and a right atrial mean pressure of 18 mm. Hg. QRS in V_1 is of very small amplitude and onset of intrinsicoid deflection is delayed. The S waves are prominent in the remaining V leads.

and moderate (one or less mercurial per week) in 20.

Distension and Pulsation of Neck Veins. Twenty-nine (48.3 per cent) patients had definite distension of these veins in the sitting position, but only seven (11.7 per cent) had associated systolic pulsations. As will be seen subsequently, patients with pulsating neck veins had a higher mean and wider pulse pressure in the right atrium than those without.

Edema of the ankles or pretibial region of slight degree was present on admission in 22 (36.7 per cent) patients. Treatment with a low salt diet and mercurial injections resulted in disappearance of the edema in all prior to cardiac catheterization.

Ascites was present on admission in 11 (18.3 per cent) patients. Only three gave a history of chronic recurrent ascites that required frequent paracenteses for control.

Murmur of Tricuspid Insufficiency, that is a systolic murmur loudest at the lower left border of the sternum and of different quality than the apical murmur of mitral insufficiency, was infrequently found. In all 11 (18.3 per cent) patients with such a murmur the clinical diagnosis of tricuspid insufficiency was made.

Jaundice was observed in only two patients. Their plasma bilirubin was 2.9 and 3.4 mg. per 100 cc. Both had advanced signs of tricuspid insufficiency.

Orthopnea of variable degree was present in 50 patients (83.4 per cent) and was not related to the degree of tricuspid insufficiency as estimated either clinically or physiologically. Of the 10 patients (16.6 per cent) without orthopnea only one had classic clinical signs of tricuspid insufficiency.

Cyanosis was present in only eight (13.3 per cent) patients.

Clinical Diagnosis of Tricuspid Insufficiency was made in only 14 (23.3 per cent) patients. All had two or more of the following signs: systolic pulsation of the veins and liver, ascites, murmur of tricuspid insufficiency.

Electrocardiographic Alterations

Electrocardiograms were available in 58 cases with complete unipolar leads in 53. In 32 (60.4 per cent) of the tracings, QRS in lead V_1 was less than 7 mm. (0.7 millivolts) in amplitude (figs. 3 and 4). This incidence of a low amplitude QRS in V_1 was statistically significant ($p < 0.01$) as compared with a group of 15 patients with mitral stenosis, auricular fibrillation and no tricuspid insufficiency, in which the change occurred only once. It was found only twice in a group of 20 patients with mitral

stenosis and normal sinus rhythm. The small complex in V_1 was of the rsR′ or incomplete right bundle branch block pattern in 14 instances (fig. 3).

The onset of the intrinsicoid deflection was normal (less than 0.03 second) in 14 (26.4 per cent) cases and prolonged on the average to 0.051 second in 39 (73.6 per cent). The average time for the whole series, 0.041 second, was longer than the average time of 0.027 second found in 15 patients with mitral stenosis, auricular fibrillation and no tricuspid insufficiency.

Right axis deviation was present in 25 (43.1 per cent). Eighteen (34 per cent) had a typical[10] or highly suggestive pattern of right ventricular hypertrophy. In 31 (58.5 per cent) the S waves were prominent in four or more precordial leads.

Roentgenograms and Angiocardiograms

Right atrial enlargement of moderate to giant degree was present in 50 (84.7 per cent) instances. It was slight in the remaining cases. Overall cardiac enlargement was the rule and in general a close relationship between the size of the atrium and degree of cardiac enlargement was found (fig. 5).

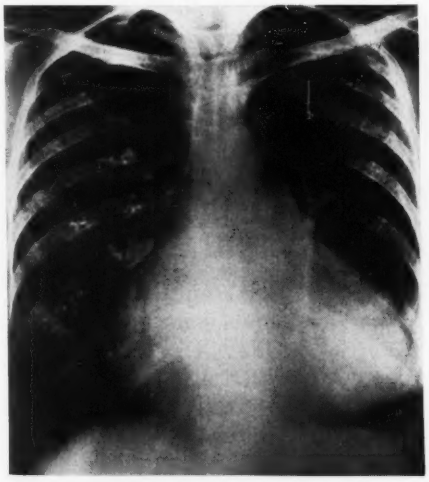

FIG. 5. Posteroanterior roentgenogram of the chest of a 43 year-old female with severe mitral stenosis, tricuspid insufficiency, auricular fibrillation, hepatomegaly, previous right-sided failure and orthopnea. Right atrium and right ventricle are markedly enlarged. Note right border of large left atrium within right atrial shadow.

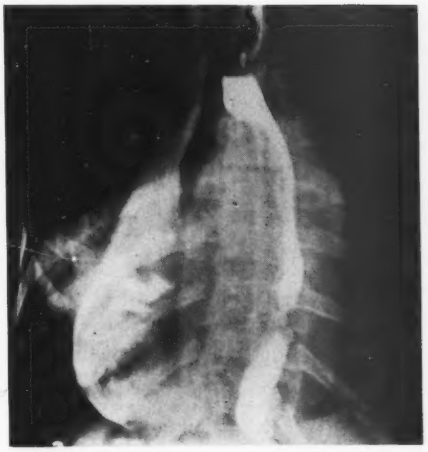

FIG. 6. Angiocardiogram of a 45 year-old female with marked mitral stenosis, aortic valvular disease, severe tricuspid insufficiency and atrial fibrillation. Contrast medium filling the very large right atrium is diluted and broken-up into islands by blood regurgitating through the tricuspid valve ("jet sign"). Barium-filled esophagus is displaced laterally by left atrium which protrudes beyond right atrial border.

The angiocardiograms confirmed these findings with one exception; a right atrium considered to be slightly enlarged in the conventional roentgenograms was found to be within normal limits. The angiocardiographic "jet sign" (fig. 6), a filling defect produced in the opacified right atrium by the regurgitant blood stream,[11] was found in only seven of the most severe cases. In all instances the angiocardiograms revealed a large left atrium, distended pulmonary veins and arteries—the pulmonary congestive phenomena typical of advanced mitral disease. Angiocardiography was of aid in distinguishing between right and left atrial enlargement, particularly in those cases in which the left atrium protruded so far to the right as to form most of the right cardiac border and thereby obscure the true size of the right atrium (fig. 6).

Hemodynamic Data

A right atrial pressure curve with the typical pattern of tricuspid insufficiency and two normal tracings are shown for comparison in fig-

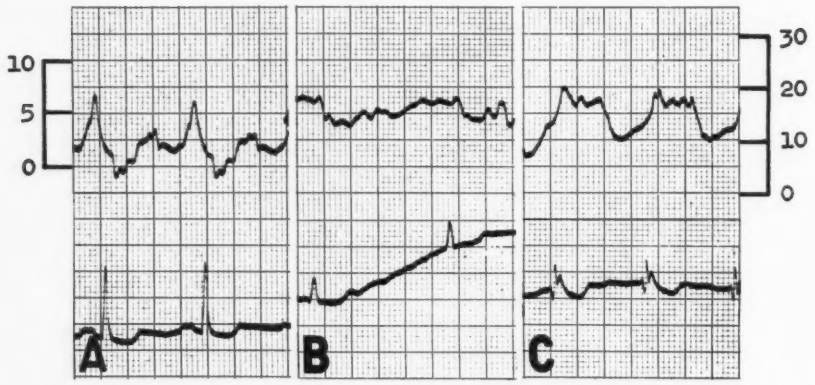

FIG. 7. Right atrial tracings and simultaneously recorded lead II from patients with mitral stenosis. In *A*. atrial contraction wave (normal rhythm) is followed by a sharp decrease in pressure occurring during ventricular systole. In *B*. atrial systole is absent (auricular fibrillation) and decrease in pressure during systole is less pronounced. In *C*. decrease of pressure during ventricular contraction is replaced by a sharp increase in pressure that persists throughout systole and has a peak-plateau contour characteristic of tricuspid insufficiency. Calibration in mm. Hg. Left scale applies to *A*. and *B*.; right to *C*.

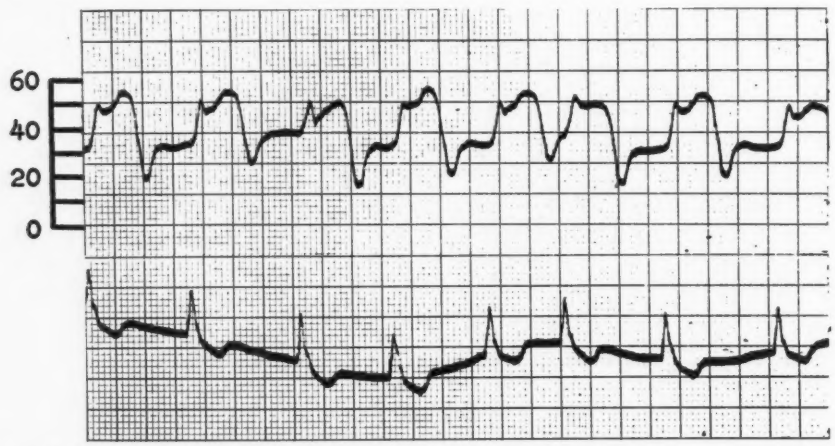

FIG. 8. Right atrial pressure tracing and lead II during exercise from a 39 year old male with advance mitral stenosis and organic tricuspid insufficiency (autopsy). The dome of the regurgitant wave reaches a level of 53 mm. Hg.

ure 7. In the normal tracings there is a definite decrease in pressure during ventricular systole produced by descent of the base of the heart. In tricuspid insufficiency, instead of a decrease in pressure during ventricular systole there is an increase produced by blood regurgitating into the atrium. This positive pressure wave persists throughout systole and has a peak-plateau[3] or more frequently a peak-dome contour. Its crest attained a level of 43 mm. Hg during the resting state and 53 mm. Hg during exercise in one of the patients in this series (fig. 8). The invariable increase in height of the regurgitant pressure wave during exercise was often helpful in confirming a pattern of tricuspid insufficiency that was not very definite at rest (fig. 9).

In table 1 the hemodynamic data obtained in the 60 patients with tricuspid insufficiency is statistically compared with similar data from

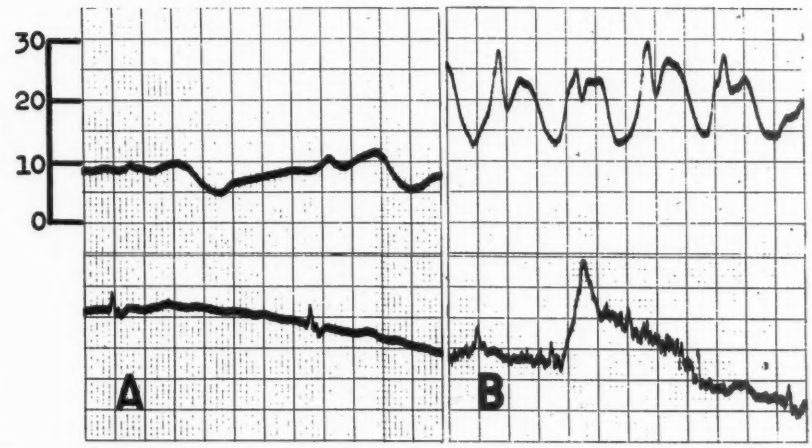

FIG. 9. Right atrial pressure tracings and lead II during rest (*A.*) and exercise (*B.*) from a 48 year old female with tight mitral stenosis. The tracing at rest is suggestive but not diagnostic of tricuspid insufficiency. During exercise pressure increases briskly and characteristic contour appears.

TABLE 1.—*Hemodynamics in Mitral Disease. Comparison of a Group of 60 Patients With Tricuspid Insufficiency and a Group of 20 With Auricular Fibrillation and No Tricuspid Insufficiency*

	T.I.		No T.I.		Significance of Difference Between Means: p
	Mean and std. deviation	Range	Mean and std. deviation	Range	
Cardiac output, L./min./sq.M. B.S.A.					
Rest	1.94 ± 0.42	1.15–3.11	2.03 ± 0.21	1.48–3.19	$<0.5 > 0.4$*
Exercise	2.29 ± 0.62	1.16–6.25	2.72 ± 0.30	1.92–3.59	$<0.02 > 0.01$
Right ventricular pressure, mm. Hg					
Rest	75/8 ± 28/5	26–136/2–23	45/5 ± 18/2	26–94/0–9	<0.01
Exercise	93/12 ± 32/5	40–140/5–25	64/5 ± 25/4	30–101/0–13	$<0.5 > 0.02$
Right atrial mean pressure, mm. Hg					
Rest	10 ± 6	3–29	4 ± 2	0–8	<0.01
Exercise	16 ± 8	6–47	6 ± 2	3–10	<0.01
Pulmonary vascular resistance, dynes-sec.-cm.$^{-5}$					
Rest	643 ± 493	110–2105	286 ± 154	117–594	<0.01
Mitral valve area, sq. cm.	0.9 ± 0.4	0.5–2.0	1.0 ± 0.3	0.6–1.8	$<0.4 > 0.3$*

* Not significant.

20 patients with mitral disease, auricular fibrillation and no evidence of tricuspid insufficiency. The mean calculated mitral valve orifice area was the same in both groups. Pulmonary vascular resistance was significantly higher in the tricuspid insufficiency group. The mean right atrial pressure in those with tricuspid insufficiency was 10 mm. Hg at rest and 17 mm. during exercise. Both values were definitely higher than those in the group without tricuspid insufficiency, in which the resting value was 4 mm. and 6 mm. during exercise. Cardiac output during exercise tended to be lower in the group with tricuspid insufficiency.

An attempt was made to determine whether there is any relation between the mean pressure or pulse pressure in the atrium and the appearance of systolic pulsations of the neck

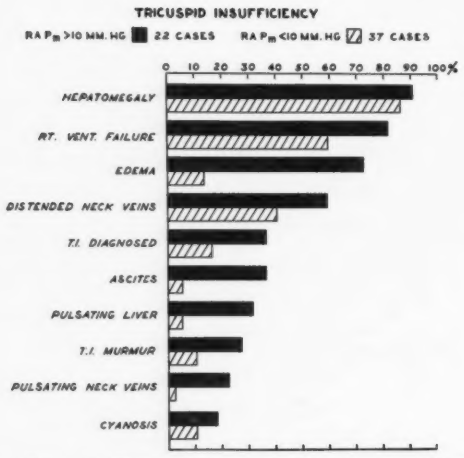

FIG. 10. Comparison of incidence of clinical features in 22 cases of tricuspid insufficiency with mean right atrial pressures greater than 10 mm. Hg and 37 cases with pressure less than 10 mm.

veins and liver. The mean atrial pressure (14 ± 8 mm. Hg) and pulse pressure (11 ± 6 mm. Hg) in the group with pulsation of the veins and liver were greater than in those without these signs, in whom mean pressure was 9 ± 5 mm. and pulse pressure 7 ± 3 mm. Both differences were statistically significant ($p < 0.01$ and $p < 0.02 > 0.01$, respectively). The clinical diagnosis of tricuspid insufficiency was made more often when both these pressures were high.

Since venous hypertension is an essential feature of tricuspid insufficiency, it was considered worthwhile to compare the clinical features of 22 patients with mean atrial pressures greater than 10 mm. Hg (a definitely elevated level corresponding to 136 mm. H_2O) with 37 whose pressures were below this level. There is a definite trend for the various manifestations of the disease to be more frequently encountered in the group with higher pressures (fig. 10). The difference in incidence of these signs in the two groups was statistically significant in the case of edema ($p < 0.01$), ascites ($p < 0.01$), liver pulsation ($p < 0.02 > 0.01$) and pulsation of the neck veins ($p < 0.05 > 0.02$). Also the pulmonary vascular resistance was greater in the group with higher atrial pressures ($p < 0.02 > 0.01$).

COMMENTS

The right atrial pressure tracings of full· 41.6 per cent of patients with chronic rheumati· heart disease and advanced mitral valvular in· volvement were found to be diagnostic of tr· cuspid insufficiency. What proportion had o· ganic alterations in the valve as opposed to purely functional insufficiency cannot be state· with certainty since it is difficult to distinguis· the two conditions by either clinical or physi· logic means. Only in the rare case in whic· signs of tricuspid stenosis accompany those o· insufficiency is an organic lesion of the valv· certain. The problem is somewhat complicate· by the fact that an early tricuspid diastoli· murmur may occur in functional tricuspid in· sufficiency.[12]

It has been suggested that a regurgitant wave of very large amplitude in the right atrial pressure curve is indicative of organic tricuspid disease.[13] In some of our patients the magnitude of the right atrial pressure and the severity of the clinical picture did indeed suggest an organic lesion. Autopsy in one revealed definite chronic rheumatic tricuspid valvulitis. In another, however, the tricuspid leaflets were normal and in a third they were only slightly thickened. Of four patients with moderate or severe clinical and physiologic tricuspid insufficiency studied at necropsy by Müller and Shillingford[12] only one had rheumatic disease of the valve. The others demonstrated hypertrophy and dilatation of the right atrium and ventricle and a dilated valve ring.

Organic tricuspid disease is by no means rare. It has been found in almost one third of the cases of chronic rheumatic heart disease studied at autopsy.[14-20] A mitral lesion was present in 90 per cent of the cases but in only 23 per cent did it occur as an isolated lesion.

Multiple factors contribute to the development of functional tricuspid insufficiency or the aggravation of a minor organic leak in severe mitral stenosis. Obstruction at the mitral orifice and pulmonary arteriolar sclerosis combine to produce a degree of pulmonary arterial and right ventricular hypertension that is more pronounced than in most other forms of acquired heart disease.[4, 5, 21-23] Stretching of the tricuspid valve ring follows the inevitable hyper-

trophy and dilatation of the right ventricle that has been chronically subjected to such a large work load and perhaps damaged by previous rheumatic myocarditis. In this regard it is significant that the patients with tricuspid insufficiency had higher pulmonary vascular resistances and right ventricular pressures than those without insufficiency but with atrial fibrillation and a similar degree of mitral stenosis. Because of the magnitude of the pressure gradient across the tricuspid valve during ventricular systole, a large regurgitant flow may occur through a relatively small insufficient orifice.[24] Once established, tricuspid insufficiency adds another load on the right ventricle.

The occasionally transient nature of functional tricuspid insufficiency has been recognized clinically for many years[25, 26] and has been confirmed by Bloomfield and associates, who demonstrated in some patients reversion of the configuration of the right atrial pressure curve from one characteristic of tricuspid insufficiency during cardiac failure to normal after compensation was restored.[3] However, there would appear to be a point in the course of a patient with mitral stenosis when dilatation of the right ventricle and tricuspid valve ring is so advanced that normal valvular function is not restored with compensation.

Auricular fibrillation, which was present in almost all of our patients, undoubtedly plays a role in the development or aggravation of functional tricuspid insufficiency. Little[27] has demonstrated that atrial systole is essential to normal closure of the atrioventricular valves. Atrial systole creates an increase in pressure that is transmitted to the ventricle. Transmission of this pressure wave is so delayed that it is at its peak in the right ventricle when the atrium is relaxing. A gradient of pressure from ventricle to atrium is thus established and is sufficient to produce adequate closure of the valve just prior to the onset of ventricular systole. When the ventricle contracts without a preceding atrial systole, the valves swing close with a hinge-like movement during early systole. Because of this delay in closure, regurgitation through the incompletely approximated valve edges occurs readily.

Frequent organic deformities of the valve, dilatation of the valve ring, auricular fibrillation and severe modifications of the pulmonary circulation appear to contribute to the high incidence of tricuspid insufficiency in mitral stenosis. The respective importance of each of these factors in the individual patient cannot be readily assessed.

In 1868 Duroziez[28] stated that involvement of the tricuspid valve is suggested when a cyanotic patient with distended neck veins, at times with edema and ascites, is able to maintain recumbency without discomfort. If to such a description is added auricular fibrillation, systolic pulsation of the liver and neck veins and a systolic murmur at the lower left sternal border, the unequivocally diagnostic picture is completed. The present evidence, however, clearly indicates that almost all of these signs occur with relative infrequency and that they are most apt to be present in patients with very high right atrial pressures and severer degrees of regurgitation. If the diagnosis of tricuspid insufficiency is dependent on recognition of these features, it will be made in only one fourth of the cases with definite physiologic manifestations of the lesion.

The high incidence of orthopnea among our patients deserves comment. All patients had mitral stenosis with the hemodynamic and roentgenographic alterations in the lungs and the pulmonary symptoms characteristic of this lesion. Why tricuspid insufficiency should cause disappearance of orthopnea when other clinical and physiologic evidences of severe mitral stenosis persist is not readily explained. Certainly the majority of the patients with severe tricuspid insufficiency manifested considerable orthopnea. Among those without this symptom only one had the other associated classic features of severe tricuspid insufficiency.

The transient nature of the murmur of tricuspid insufficiency, the difficulty in distinguishing it from the murmur of mitral insufficiency, its accentuation by inspiration have been noted in the literature.[7, 12, 29] The murmur is not always accentuated by inspiration when mitral disease coexists.[12] Although it is usually heard best along the left sternal border in the fourth and fifth intercostal spaces, it can be

heard above this point or close to the apex.[12] The systolic murmur attributed to mitral insufficiency in a number of our patients in whom no evidence of mitral insufficiency was found at surgery could have been due to tricuspid insufficiency.

In contrast with the infrequency of the classic signs of tricuspid insufficiency, auricular fibrillation, persistent enlargement of the liver and increased size of the right atrium were the most constant findings. These signs in a patient with rheumatic mitral disease who has a history of previous right-sided failure that has required mercurial administration for control should suggest the diagnosis of tricuspid insufficiency. The sheer frequency of the lesion in patients with auricular fibrillation lends considerable support to such a diagnosis.

A QRS complex in V_1 of small amplitude (i.e., less than 0.7 millivolt) and with a delayed onset of intrinsicoid deflection is the electrocardiographic feature that most consistently and with great statistical significance distinguishes patients with mitral disease and tricuspid insufficiency from those without insufficiency of the tricuspid valve. In a number of instances the small QRS in V_1 was of rsR′ configuration, which together with the delay in intrinsicoid deflection constituted the pattern of incomplete right bundle branch block. Because of the many factors influencing the electrocardiogram in this situation, it is not possible to state that tricuspid insufficiency alone is responsible for these alterations. However, in 62.6 per cent of 50 patients with autopsy-proved tricuspid insufficiency Aceves and Carral[14] also found the onset of intrinsicoid deflection in V_1 and V_2 to be prolonged beyond 0.04 second. In other publications an incidence of 47 to 65 per cent of right bundle branch block has been cited.[30, 31]

According to Cabrera and Monroy,[32] the characteristic electrocardiographic pattern associated with a lesion that produces diastolic overloading of the right ventricle (i.e., interatrial septal defect) in contrast to one producing systolic overloading (i.e., pulmonic stenosis) is complete or incomplete right bundle branch block. Tricuspid insufficiency is a diastolic overloading lesion. Electrocardiograms taken before and after the onset of tricuspid insufficiency in a patient with mitral stenosis and published by these authors demonstrate a decrease in the voltage of QRS in V_1 from 0.9 to 0.4 millivolt after the tricuspid regurgitation had developed.[32]

Persistent hepatomegaly, enlargement of the right atrium and many of the other signs of tricuspid insufficiency are essentially the result of right atrial and systemic venous hypertension. Since right ventricular failure may produce these changes, their diagnostic usefulness may be questioned. The fact remains, however, that the right atrial and venous pressures are chronically and persistently higher (in tricuspid insufficiency, despite vigorous cardiac therapy) than when the valve is competent. Continued elevation of the venous pressure and signs thereof after full cardiac compensation is achieved can be regarded as presumptive evidence of a tricuspid lesion.

By its congestive effect on the venous system and consequent elevation of hydrostatic pressure in the venules and capillaries, tricuspid insufficiency is conducive to the development of edema even if the right ventricle is functioning normally. Aside from increasing filtration of fluid through the peripheral capillaries venous hypertension promotes edema in other ways. There is evidence that elevation of the renal venous pressure above 150 mm. H_2O is followed by a decrease in excretion of sodium and water because of augmented tubular reabsorption.[33] More recently it has been demonstrated that congestion of any sizable segment of the peripheral venous bed induces similar changes in renal function.[34-36] Objection has been raised to the application of these observations to the problem of edema in chronic cardiac failure because of the acute nature of the experiments. However, the marked and brisk rise in atrial and venous pressures that occurs with even mild exercise in tricuspid insufficiency represents an acute experiment that may be repeated many times in the course of the patient's day. These considerations are important in explaining the ease with which patients with tricuspid insufficiency accumulate

edema and the frequency of mercurial diuretic administration required for its control. We have therefore applied the term right-sided failure rather than right ventricular failure to patients with tricuspid insufficiency.

There is a need for the recognition of factors that may limit the beneficial effects of corrective surgical procedures on the mitral valve. Tricuspid insufficiency is such a factor. We have seen occasional patients with mitral stenosis and severe tricuspid insufficiency who had some relief of pulmonary symptoms after mitral valvuloplasty but who continued to manifest signs of tricuspid insufficiency and recurrent edema and ascites. Although it is not a contraindication to the operation, the impression is that patients with tricuspid insufficiency do not improve either hemodynamically or clinically after mitral valvular surgery as well as those without the lesion. An adequate and long term evaluation of many patients is needed before this impression can be substantiated. Such a study is thwarted from the start if the tricuspid insufficiency with its distinct hemodynamic effects is not recognized preoperatively.

Summary

Of 146 patients with rheumatic heart disease and predominant mitral valve involvement studied by cardiac catheterization, 60 were found to have a right atrial pressure curve characteristic of tricuspid insufficiency. The clinical diagnosis had previously been made in only 23.3 per cent of the cases. All the patients who had cardiac failure were under optimum medical control at the time of the study.

The most constant clinical features were auricular fibrillation, persistent liver enlargement, a history of right-sided failure and roentgenographic evidence of moderate to severe enlargement of the right atrium. A small QRS complex, frequently of the rsR′ pattern, in lead V_1 of the electrocardiogram was found in 60.4 per cent of the cases.

The pulmonary vascular resistance, right atrial mean and right ventricular pressures were distinctly greater as compared with the values in a group of patients with auricular fibrillation, a similar degree of mitral involvement but no tricuspid insufficiency.

The classical clinical features of tricuspid insufficiency were present relatively infrequently and were seen more often in patients with right atrial mean pressures greater than 10 mm. Hg.

Tricuspid insufficiency, functional or organic, is a frequent complicating lesion in mitral valvular disease and its presence should be suspected in any case with auricular fibrillation, persistent liver enlargement and definite increase in size of the right atrium.

Summario in Interlingua

In 60 inter 146 patientes de cardiopathia rheumatic e predominante affection del valvula mitral, un studio a catheterisation cardiac revelava un curva de pression dexteroatrial del typo characteristic de insufficientia tricuspide. Iste diagnose habeva previemente essite establite per medios clinic in solo 23,3 pro cento del casos. Omne le patientes con insufficientia cardiac esseva sub optime surveliantia durante le studio.

Le plus constante tractos clinic esseva fibrillation auricular, persistente allargamento hepatic, un historia de insufficientia del latere dextere, e evidentia roentgenographic de moderate o sever allargamento del atrio dextere. In 60,4 pro cento del casos nos constatava un parve complexo QRS—frequentemente del configuration rsR′—in le derivation V_1 del electrocardiogramma.

Le resistentia pulmono-vascular, le pression median dexteroatrial, e le pression dexteroventricular esseva distinctemente plus grande que in un gruppo de patientes con fibrillation auricular, un simile grado de affection mitral, sed nulle insufficientia tricuspide.

Le classic characteristicas clinic de insufficientia tricuspide esseva relativemente infrequente e se monstrava predominantemente in patientes con pressiones median dexteroatrial de plus que 10 mm Hg.

Insufficientia tricuspide—o functional o organic—es un frequente complication in casos de morbo del valvula mitral. Su presentia debe esser suspectate in omne casos monstrante fibrillation auricular, persistente allargamento

hepatic, e definite augmento del dimension del atrio dextere.

ACKNOWLEDGMENT

We are very grateful to Misses Dolores Lukas and Elaine Hornberger for their technical assistance, to Dr. Jorge Araujo for his assistance with many of the catheterizations and to Dr. Israel Steinberg for making the angiocardiograms available to us.

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The Surgical Relief of Aortic Stenosis by Means of Apical–Aortic Valvular Anastomosis

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(With the Technical Assistance of PHILIP E. WAITHE)

A means has been devised whereby the aortic valve can be effectively by-passed. Left ventricular blood leaves via the apex through a lucite tube in continuity with a modified Hufnagel valve and then enters the thoracic aorta. In dogs so treated the ascending arch of the aorta may be totally and permanently occluded without apparent impairment of the circulation. Postoperatively these dogs run, jump and swim and are not readily distinguishable from normal dogs. The entire ventricular manipulation is completed in 30 to 60 seconds. The applicability of this procedure to the alleviation of aortic stenosis in man is discussed.

THE basic defect in aortic stenosis is a mechanical or hydraulic one involving a small cross-sectional area in the outflow tract of the left ventricle. This results in high intraventricular systolic and low aortic systolic and pulse pressures. The main physiologic derangement, a low and limited cardiac output, is attributable to the high outflow resistance which greatly increases the ventricular work load in the presence of a low coronary perfusion pressure. Coronary vasodilation can compensate for the imbalance between ventricular work and low coronary perfusion pressure up to a point, but when this compensatory mechanism has been fully utilized, circulatory compromise results.[1] The reader is referred to the writings of Gorlin and his associates for a detailed analysis of the hydraulic factors in this disease.[2]

The objective of any procedure aimed at correcting the derangement produced by aortic stenosis should, accordingly, be aimed at decreasing the left ventricular work load, increasing coronary perfusion pressure or, preferably, both. Any measure which substantially decreases the resistance to the outflow of blood from the left ventricle will accomplish this as long as it does not at the same time produce regurgitation or increase that which may already be present.

Unlike the heartening progress made in correcting stenosis of the mitral valve, a direct attack on the stenosed aortic valve has carried with it a high operative mortality and less convincing improvement in those who survive.[3, 4, 5]

If a direct attack on the aortic valve is to be avoided it is apparent that some other avenue of egress from the ventricle to the aorta must be provided. A connection between the ventricular apex and thoracic aorta appeared to be the method of choice. The apex was chosen as the site for left ventricular intubation for the following reasons. (1) It appears to be the least irritable area. (2) It is the least vascular area, and it does not compromise tissue distal to it if its vessels are cut across. (3) The ventricular wall is thinnest at the apex. (4) A tube placed through the apex lines up neatly with the long axis of the left ventricle and thus provides the most hydraulically desirable outflow tract.[6] It also precludes obstruction of the inlet end of the tube by the septum during systole.

The results of earlier acute experiments were described in a brief preliminary note.[7] These appeared to justify the more serious attempts of improving the technique and

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Presented in part before the Department of Surgery, Kantonspital, Zurich, Switzerland, March 11, 1954 and the Second World Cardiology Congress, Washington, D. C., September 17, 1954.

Supported by a grant-in-aid from the Greater Boston Chapter of the Massachusetts Heart Association and The Vincent Astor Foundation.

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initiating survival experiments. Since that time, effort has been devoted to developing a prosthesis which makes a comfortable fit between the ventricular apex and thoracic aorta. A method has also been developed for introducing the prosthesis into the ventricle which (A) involves little or no blood loss, (B) requires only 30 to 60 seconds for its completion, (C) eliminates the hazard of left ventricular and coronary artery air embolus, (D) assures that the insertion is made precisely into the ventricular apex through the apical dimple, and (E) may be done, if desirable, without the use of any myocardial sutures.

Procedure

Instruments. The valve prosthesis used in these experiments is shown in figure 1.* The ventricular end has an inside diameter of 11 mm., (cross-sectional area 0.95 cm.²) and an outside diameter of 12 mm. The ventricular end of the tube is 16 mm.† long and it is this segment which extends from the external surface of the apical myocardium well into the lumen of the ventricular cavity. Just distal to this segment there is a small ridge which rests on the epicardium and there is also a freely rotating spoked wheel. The latter is used to affix sutures to the myocardium, the pericardium or both. After the tube curves and leads the blood through a valve of the Hufnagel[8] type, it leads to the wide-angled, Y-shaped aortic end. One end of the Y tube conducts blood cephalad, the other caudad. The internal diameter of each arm of the Y tube is 10 mm.; the outside diameter is 12 mm. Two grooves are present on each arm of the Y tube; a number 2 silk tie fixes the aorta in the proximal groove and a Hufnagel[8] nylon, multiple point suspension ring fixes it in the distal groove. (See fig. 2.)

The instruments required to perform the apical-aortic anastomosis (AAA procedure) as outlined below are shown in figure 2. The *introducer* (2C) is a curved stainless steel tube bent to the shape shown with a handle on it. The apical end of the introducer has on it a lucite bulb the end of which in turn is capped with a rubber piece fixed onto it with a silk ligature. A stylet runs the length of the tube and terminates in a long, sharp, trocar point which emerges 35 mm. from the apical end of the introducer when pressure is made on the stylet button.

The *apical retraction ring* (2C) is used to retract the apex of the left ventricle back over the end of the introducer as the latter seeks the internal apex. This simple ring serves three highly important functions. First, it prevents the dislocation and overstretching of the heart and ventricle; this abolishes or greatly diminishes the arrhythmias which are observed if it is not used. Secondly, it stretches an isolated segment of the apex over the end of the introducer, steadies it, and delineates the precise spot (apical dimple) where the myocardial hole is to be cut. Lastly, it enables the introducer to be gently and precisely persuaded through the small hole cut in the apex by coning the apex down over the tip of the introducer.

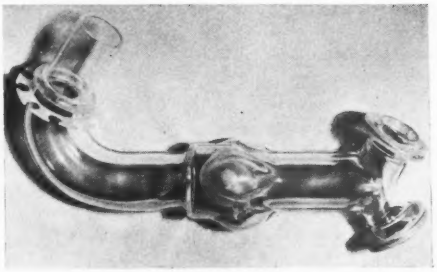


Fig. 1. Valve prosthesis used in the apical-aortic anastomosis procedure. See text.

The *apical circumcision knife* is an 8-mm. dermatology biopsy punch renamed for this purpose. The only way in which it has been altered is the provision of a hole up its middle long enough to accept the full length of the pointed stylet after the latter has emerged from the end of the introducer and has pierced the apex (2C).

The *aortic clamp approximator* is shown in figure 2B. Its function is simply to draw together and maintain parallel the two Gross aorta clamps after the latter have occluded the thoracic aorta, thus providing a slack rather than a taut aorta during the intubation of that vessel. In principle it is similar to the Bradshaw clamp but is simpler, and in the hands of the authors, appreciably more rapid and convenient to use.

Steps in the Procedure. (1) Under Nembutal anesthesia and intermittent positive pressure breathing, the sixth rib is removed with the dog in the right lateral position. The artificial respiration device (Starling pump) is so adjusted by means of a screw clamp resistance on the expiratory line that there is an end-expiratory pressure of at least 4 cm. H_2O. Permitting the lungs to collapse further than this during expiration produces arterial hypoxia

(2) The right and left intercostal arteries, 1 through 5, are ligated, divided, and the aorta mobilized.

(3) The nylon clip, shown in figure 2A, is then put in place across the ascending arch of the aorta 2 to 3 cm. above the aortic valve and proximal to the brachiocephalic artery. This clip is to be permanently closed immediately after the AAA

* The authors are indebted to Mr. Carl Hewson, Brunswick Mfg. Co. for the fabrication of the prosthesis.

† This has been shortened to 13 mm. in a later series.

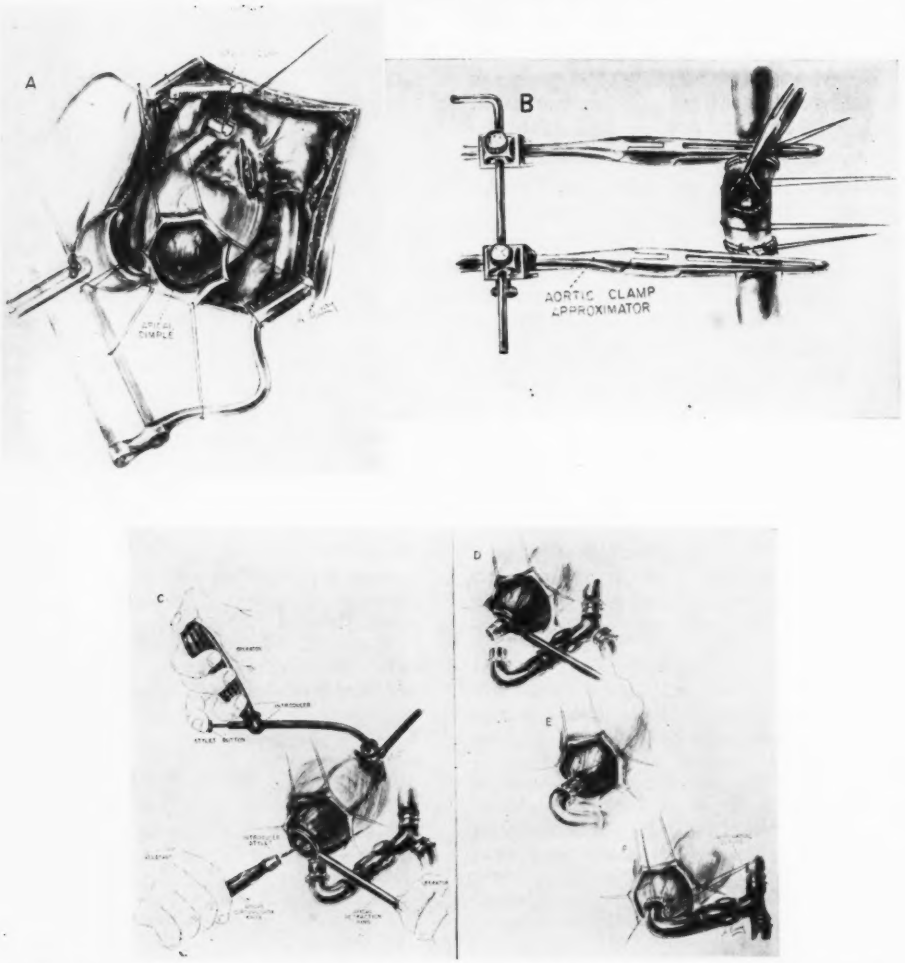


FIG. 2. (*A*) Aorta is mobilized, the pericardial aperture is formed, the pericardium is slit over the left atrium and the nylon clip is in place on the ascending aortic arch. Note the apical dimple, a whitish, dimpled spot which is clearly present in about three out of four dogs. When not clearly present visually, its location can be ascertained by exploratory dimpling with the tip of the fifth finger. It signals the precise location of the true left ventricular apex. The phrenic nerve has been omitted. (*B*) Gross aorta clamps on the thoracic aorta are drawn together with the aortic clamp approximator, producing slack in the segment to be intubated with the Y end of the valve prosthesis. Multiple-point suspension rings and ligatures are in place. (*C*) Valve prosthesis intubation into aorta has been completed and prosthesis filled with saline and stoppered. Introducer has been placed into left ventricle via the left atrium and the apex is drawn over the end of introducer with the apical retraction ring. The introducer stylet has been made to pierce the apical dimple by pressure on the stylet button. Assistant is preparing to slide the apical circumcision knife over the stylet and cut out plug of myocardium. (*D*) Myocardial plug has been cut and removed and stylet has been retracted. Stopper has been removed from the prosthesis and the coupling of it to the introducer begun. Not shown is the catheter which plays a stream of saline into the prosthesis as the coupling proceeds. (*E*) The prosthesis has been coupled onto the introducer and is being drawn into the left ventricle. (*F*) Ventricular intubation is completed. Myocardial sutures are being affixed to the spoked wheel.

procedure is completed, thus insuring that total cardiac output (minus coronary flow) will leave the ventricle via the apical route.

(4) A pericardial aperture is formed by incising the pericardium near the apex and retracting it with sutures tied to the Balfour retractor as shown in figure 2A.

(5) A second pericardial incision is made lateral to the left phrenic nerve over the site of the left atrium. The atrial appendage is then picked up, and the noose of a Rumel tourniquet slipped over it and slid well down over the atrium, care being taken not to impinge on the left circumflex coronary artery. The appendage is opened, picked up in four fine hemostats and the trabeculae cleared so as to permit the ready insertion of the introducer.

The foregoing steps are completed in an unhurried fashion. The subsequent sequence, however, should be performed expeditiously so as to, (a) keep the time of total thoracic aortic occlusion under 10 minutes, and (b) limit the time of the ventricular intervention.

(6) Two Gross aorta clamps are placed 8 to 10 cm. apart on the thoracic aorta and closed. They are then brought closer together and fastened in place with the aortic clamp approximator so as to give the aorta some slack and thus facilitate the introduction of the Y end of the prosthesis into it. The aorta is then transected between the clamps and with the help of fine hemostats, the aortic intubation is completed. The use of the aortic clamp approximator (fig. 2B) has made this part of the procedure easy instead of troublesome. A number two silk ligature ties the aorta securely in each proximal groove and a multiple point suspension ring fixes the aorta in each distal groove (fig. 2C). The prosthesis is then filled with saline through a catheter inserted in the ventricular end. When the air has been exhausted therefrom, a soft rubber stopper is placed in the ventricular end of the prosthesis and the aortic clamps removed, thus permitting resumption of aortic flow. In the last seven operations performed, the time of thoracic aortic occlusion varied from five and four tenths to eight and four tenths minutes with a mean of six and nine tenths minutes. This is comfortably under the critical limit for avoiding postoperative spinal cord damage.[8]

(7) The introducer is then promptly inserted into the left ventricle via the atrium, seeks the apex and has the latter drawn down over it with the apical retraction ring (fig. 2C). Pressure is then made on the stylet button causing the stylet point to pierce the apex. While the apex is thus steadied by the introducer on the inside and the retraction ring on the outside, the apical circumcision knife is slid down onto the protruding stylet (fig. 2C) and cuts out a circular plug of apex. The plug thus cut out is removed, the stylet is retracted and the introducer eased out through the apical hole with the help of gentle counter-pressure from the apical retraction ring (fig. 2D).

(8) The stopper previously placed in the ventricular tube end of the prosthesis is now removed and the tube coupled onto the soft rubber end of the introducer. The function of the soft rubber tip is to preclude the possibility of scratching the internal surface of the prosthesis (fig. 2D and E). Air is exhausted from the tube by a stream of saline from a catheter as the coupling is completed.

(9) The tube is then drawn back through the apical hole with the introducer (fig. 2E) and after the tube is well in the ventricle the introducer is disengaged from the prosthesis and gently withdrawn from the ventricle.

In the last seven operations attempted, more confidence and facility with these maneuvers was acquired. In them, without any particular sense of urgency, it was possible to complete steps 7, 8 and 9 (fig. 2C, D and E) in 24 to 65 seconds with a mean time of 46 seconds.

(10) The nylon clip previously placed around the ascending arch is tied closed with a number 2 silk ligature.

(11) The atrial appendage is doubly ligated.

(12) Three to five triple zero cotton sutures are then placed in the myocardium immediately adjacent to the tube and fixed to the spoked wheel (figs. 1 and 2F). The edges of the pericardial aperture are then affixed firmly to the spoked wheel by means of additional cotton sutures. In two of the surviving dogs the myocardial sutures were omitted and the tube held in place solely by pericardial sutures.

The end result of this procedure is a 12-mm. lucite tube in an apical hole produced by an 8 mm. circular knife. The fit is sufficiently snug to prevent leakage around the tube. The removed myocardial plug measured 5 to 6 mm. in diameter and weighed an average of 170 mg. or approximately 0.1 per cent of the estimated total heart weight.

Penicillin and streptomycin were administered for one to two weeks postoperatively. All dogs received distemper serum and vaccine.

With the exception of the 51-Kg. Great Dane described below, the dogs weighed from 18.1 to 30.8 Kg. with an average of 21.6 Kg.

Results

A total of 17 operations were attempted under aseptic conditions of which 10 were fatalities. These include early attempts which were largely failures associated with now avoidable errors but will be described both in the interests of completeness and also because some of the errors were fruitful.

Fatalities. Three dogs died of postoperative hemorrhage resulting from our early attempts

to occlude the ascending aortic arch, a part of the procedure which would, of course, not be included in the therapeutic operation. These fatalities were not helpful except in that the proper use of the nylon clip was eventually found to be a successful means of totally and permanently occluding the ascending aortic arch. The use of such a device was suggested by Hufnagel in connection with other studies.[9] One dog died of postoperative hemorrhage from an unsecured intercostal vessel in the spinal angle where the sixth rib had been removed. This was demonstrated by careful postmortem perfusion of the aorta via the left subclavian artery. One dog died of massive empyema following an obvious break in asepsis during the procedure.

The other five fatalities were more informative about the procedure itself. One occurred consequent to tearing the aorta while attempting the Y-end intubation and the subsequent hurried and poor ventricular intubation. This failure prompted the design and use of the aortic clamp approximator shown in figure 2B. After this no further difficulty was encountered on that score. One ambitious attempt was made to insert the same prosthesis used in 20-Kg. dogs into a 51-Kg. Great Dane. From this experience it became clear that it would be desirable to be provided with prostheses of different lengths if the method were to be applied clinically. One fatality occurred 25 days postoperatively. At postmortem examination it was found that hemorrhage had occurred from the cephalad aortic tube-vessel junction where one of the teeth of the multiple point suspension ring had been placed directly on and had eroded through the aortic ostium of one of the ligated intercostal arteries. Previously no particular effort had been made to avoid this. Another dog died with much the same picture at postmortem examination on the fifth postoperative day; in this dog, however, damage at the tube-vessel junction was severe enough so that it was difficult to be sure that placement of the nylon ring through an intercostal ostium was the only cause. The last fatality occurred in one of the three dogs in which no myocardial sutures were placed. The ventricular tube was held in place solely by four triple zero cotton sutures affixing the pericardium to the spoked wheel. The tube pulled out on the fifth postoperative day and it was seen that the pericardial stay sutures had been cut through by the sharp edges of the spoked wheel. The spoked wheel has since been made thicker and with smooth edges. The other two dogs with no myocardial sutures have survived.

Two of the 10 fatalities died at operation namely, the 51-Kg. Great Dane and the dog in which the aorta was torn prior to the use of the aortic clamp approximator. The other eight died on the first, first, second, fifth, fifth, seventh, ninth and twenty-fifth postoperative days.

Survivals. Seven dogs have survived from two to four months after the operation and are in robust health at the present time. The longest survivor, Clicka, has become a household pet. During a three-month stay in Vermont he frequently swam across a one-mile lake and back. He has acquitted himself creditably in several vigorous dog fights. Having been a stray and apparently not well fed, he was anemic and undernourished preoperatively, weighing 29 Kg. On a proper diet and with worming postoperatively he has gained 6 Kg. He runs rapidly, jumps 3½ foot hurdles, is playful and is, in fact, indistinguishable from a normal dog except for the clicking sound. It is clear therefore that an apical ventricular tube with a cross-sectional area of 0.95 cm.^{2} can transport sufficient flow to support vigorous activity in a 35-Kg. dog without producing overt evidence of an excessive imposition on the myocardium. It should be noted that, whereas in man resting cardiac output is approximately 75 cc. per kilogram per minute, it is approximately 125 cc. per kilogram per minute in the dog.[10, 11]

The other six dogs are in the same good health and exhibit their normal tendency to run, play and fight. It has been planned to mate the two females with two of the males to ascertain if they will be unduly handicapped by gestation.

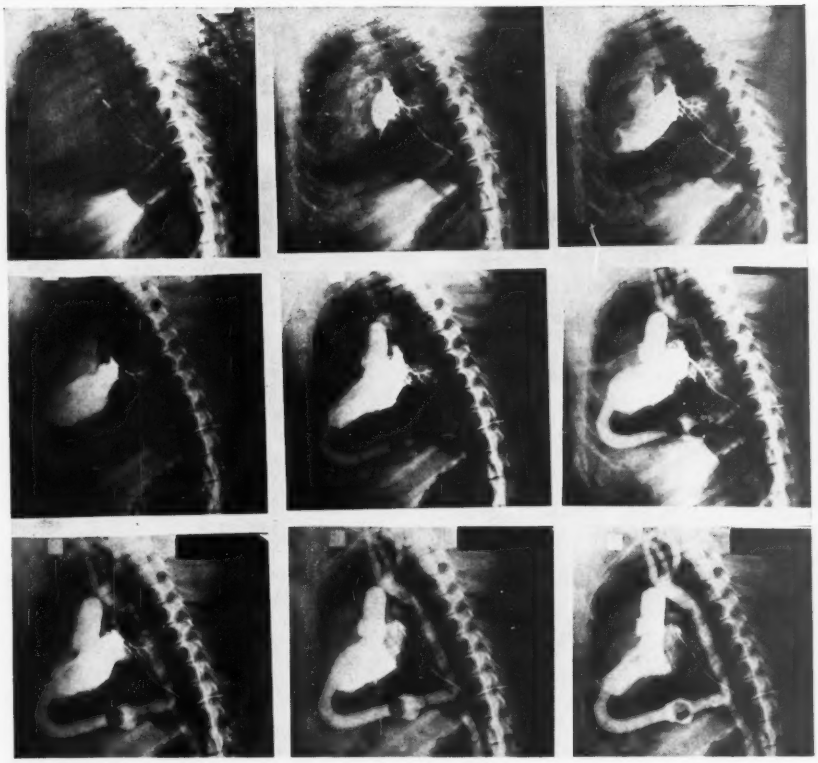


FIG. 3. Angiocardiograms taken in one of the early acute experiments in which the ascending aortic arch was stenosed with umbilical tape. Sequence progresses from top left to bottom right and is completed in two and four tenths seconds. The prosthesis used was long, with the result that the ventricular end of the tube did not coincide perfectly with the long axis of the left ventricle. It nevertheless functioned well. The catheter through which contrast medium was injected was in the left atrium or orifice of pulmonary vein. Note position of valve ball in systole in the lower right figure.

Of the last seven operations attempted, five dogs survived, one of the failures being the dog described above in which no myocardial sutures were placed.

Complications. Cardiac arrhythmias, chiefly ventricular ectopic beats, of occasional to moderate frequency, occurred in all dogs in the immediate postoperative period and lasted from one-half to approximately four days although precise observations were not made in this regard. No dog died of cardiac arrhythmias postoperatively. Ventricular fibrillation occurred during the operation in 2 of the 17 dogs. One of these was an early attempt described above, in which the aorta tore and the ventricular intubation was hurried and poorly placed. The other instance of fibrillation occurred about five minutes after the ventricular intubation while the nylon clip was being closed on the ascending aortic arch. It was noted that the myocardium was cyanotic and that the blood traversing the prosthesis was dark. The expiratory resistance and tidal volume of the respiratory pump were found to be low; these were increased and vigorous manual massage was carried out. Defibrillation was successfully accomplished on the second shock. It was of interest that the prosthesis remained securely in place during this sequence. The dog survived until the twentyfifth postoperative day, as described above. Thus, in the group of 17 dogs, only 1 succumbed to

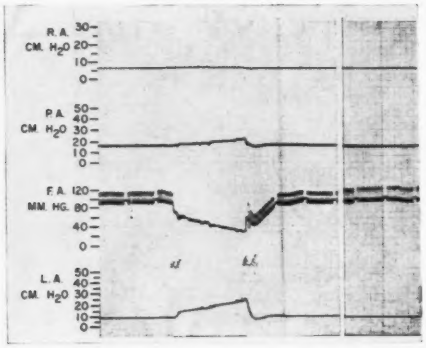


FIG. 4. Dog in which apical-aortic anastomosis had been performed and severe stenosis of ascending aorta produced. At the beginning of the left-hand tracing, the anastomosis was open. During the middle of this tracing, the anastomosis was closed (signal at bottom). Note severity of the induced "aortic stenosis." Anastomosis reopened again at end of signal. In the right-hand tracing, the anastomosis was closed, and the normal outflow tract unconstricted. Note similarity of values. R. A. = right atrium. P. A. = pulmonary artery. F. A. = femoral artery. L. A. = left atrium. R. A., P. A. and L. A. are mean pressures. F. A. shows full pulse and mean pressures at regular intervals. Time at bottom in seconds. The right hand tracing starts 20 seconds after the end of the left hand tracing. See text.

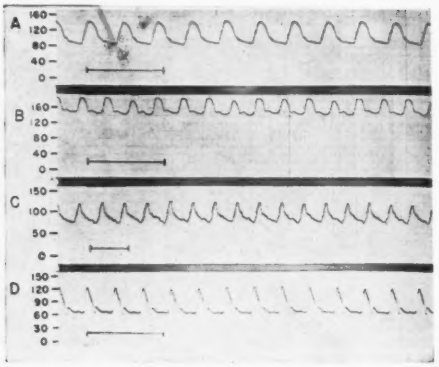


FIG. 5. Postoperative femoral arterial pressures in four dogs after apical-aortic anastomosis procedure and total occlusion of ascending aorta. Indicated time interval = 1 second on each tracing. A. Blackie, 21.4 Kg. Tracing taken immediately after operation. Survival. B. Pepper, 30.8 Kg. Tracing taken immediately after operation. Died of empyema on ninth postoperative day. C. Sybil, 21.1 Kg. Tracing taken one month postoperatively. Survival. D. Angie, 22.0 Kg. Acute preparation. Tracing taken immediately after operation.

ventricular fibrillation; and the cause for this was clear and avoidable.

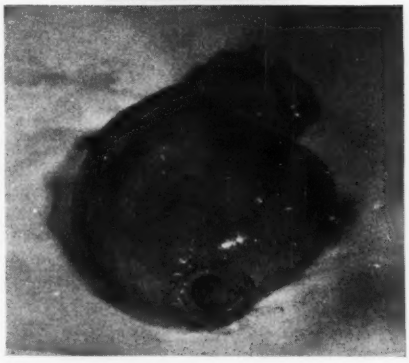
No dog succumbed from the consequences of embolization. In one of the seven surviving dogs, however, a transient period of right hind-leg coldness, lameness and absence of femoral arterial pulsation was noted on the twenty-eighth postoperative day. This episode lasted 24 hours after which the femoral pulse reappeared and no further difficulty was noted. The only other clinical evidence suggestive of embolization has been hemoglobinuria in the postoperative period. Circumscribed renal infarcts were observed at postmortem examination in some of the dogs that succumbed from thoracic hemorrhage or empyema; on the other hand hemoglobinuria was observed when subsequent postmortem observation revealed the absence of obvious infarcts. The observed discoloration of the urine was accompanied by an obvious hemoglobinemia. The nature of this observed hemolysis is being investigated by Stohlman and coworkers;[19] the results will be published in detail. These findings suggest that the red cell destruction in the dog is a result of the action of the ball valve and introduces the possibility that this action may also account for the postoperative anemias seen after the Hufnagel operation.[21]

Other Studies. Angiocardiograms were obtained in one early acute preparation in which the ascending aortic arch was tightly stenosed by umbilical tape instead of the subsequently used nylon clip. The results are shown in figure 3.

Right atrial, pulmonary artery, left atrial and femoral arterial pressures were recorded in an acute, open-chest preparation in which a segment of donor aorta was used to connect the ventricular tube-valve segment with the Y tube in the aorta. This was done so that the apical-aortic anastomotic by-pass could be closed and opened at will. Before the beginning of left hand tracing in figure 4 a severe constriction of the ascending aorta had been produced. When the apical-aortic anastomosis was closed (signal at bottom) the severity of the stenosis can be seen from the markedly lowered systolic, diastolic and pulse pressures

n the femoral artery and the marked elevation of left atrial pressure. The subsequent opening of the apical-aortic anastomotic by-pass, a crude simulation of a therapeutic intervention, resulted in the re-establishment of satisfactory levels. Perhaps of more import is a comparison of the values in the latter part of the left hand tracing with those in the right hand tracing taken 20 seconds later. In the former

A



B

FIG. 6. (*A*) Eight pounds of mercury in a flask hanging from the ventricular end of prosthesis in a dog 14 days after operation. Note fibrosis of junction. (*B*) Same heart after prosthesis was removed showing smoothly lined apical hole. Pericardium removed in both *A* and *B*.

there was almost complete stenosis of the ascending aorta and the apical-aortic anastomotic by-pass was open. In the latter the by-pass was closed and the normal aortic outflow path re-established. The difference does not appear to be great. Of particular significance is the fact that the mean left atrial pressure was less than 1 cm. H_2O higher when the cardiac output traversed the apical-aortic anastomosis as compared with the normal route.

Femoral artery pressure tracings were taken in four dogs after complete occlusion of the ascending aortic arch and the by-pass procedure was performed. These are shown in figure 5.

In addition to the above series, two dogs were studied in which another type of prosthesis was used. This was similar to the one shown in figure 1 except that, instead of having a Y tube at the aortic end, the prosthesis was connected to the thoracic aorta with a donor aortic graft by means of an end-to-side anastomosis. Just at the free end of the aortic graft, where the graft was attached to the distal end of the prosthesis, the graft perforated on the fourteenth and twenty ninth days postoperatively in the two dogs so studied.

Figure 6A shows the weight supported by the apical-tube junction 14 days postoperatively. Figure 6B shows the appearance of the apical hole in the same heart after the tube had been removed. The ventricular end of the prosthesis extends through this hole well up into the ventricle. In the dog described above which died on the twenty-fifth postoperative day, the apical-tube junction was extremely difficult to disjoin by manual traction. This was due to a firm fibrotic overgrowth of tissue which made the spoke densely adherent to the apex.

DISCUSSION

Biologically it is more attractive to alleviate a disease without the use of prosthetic devices if this can be achieved, that is, by direct attack upon and correction of the stenosed valve. There is no assurance, however, that even if the stenosed valve itself were amenable to repair, the deformity would not recur. In the relatively brief history of mitral-valve surgery, recurrence of mitral stenosis has

already been reported and it was held unlikely that the initial operation was inadequate.[12]

With the exception of a spring loaded valve or similar device, no man-made valve is known to the authors which is as free of slip or regurgitation in normal use as the aortic or pulmonic valves. The backward flow of blood required to seat the ball when the direction of the pressure gradient is reversed is undoubtedly larger than that which occurs when the normal aortic valve closes. That this amount of regurgitation is of little practical significance, however, is indicated by the above data showing the small elevations of left atrial pressure when blood leaves via the apical-aortic anastomosis instead of the normal aortic outflow tract. The marked lowering of left atrial pressure if the anastomosis is opened when "aortic stenosis" is present, is a highly significant measure of the reduced work load of the ventricle.[13]

Postmortem inspection and palpation of a severely stenotic aortic valve gives the impression that valve fracture, commissurotomy and removal of portions of the valve are a good deal more difficult to accomplish precisely and uniformly in this area than in the mitral area.[14] Further, an alteration may be made which is so extensive as to produce or significantly increase regurgitation. With the apical-aortic anastomosis procedure as outlined above, little significant regurgitation is added to what is already present, and the resistance of the new outflow tract is precisely known.

Bailey, Glover, O'Neill and Redondo-Ramirez[15] were also apparently influenced in their thinking by such considerations since, in their earlier efforts to alleviate aortic stenosis, they similarly attempted to by-pass the aortic valve. Only when "discouraged by these attempts at by-passing or replacing the aortic valve" did they redirect their effort to the direct operation. Hufnagel also reported that his attempts "have had little success."[22]

In regard to the stability of the ventricular end of the prosthesis, the authors have recently examined the hearts of four dogs three to three and one half years after operation in which a lucite tube had been placed in the anterior wall of the right ventricle.[16] This tube conducted right ventricular output to the bifurcation of the pulmonary artery via a vena-caval graft. The main pulmonary artery was tied off. The appearance of the tube and myocardium were such as to suggest that both would have continued to function well indefinitely had the dogs not been sacrificed.

In regard to the aortic end of the prosthesis, the experiences of Hufnagel[8] have demonstrated that a double-ended lucite-tube valve can be placed in the thoracic aorta in man with relative safety if the multiple point suspension ring principle is used.

The main residual hazard is that of embolization. It is Hufnagel's opinion,[17] as well as ours, that the greatest hazard is the fibrin ring that forms around the tube distal to the nylon multiple-point suspension ring at the tube-vessel junction where blood stagnates. This fibrin ring was present at the aortic tube-vessel junction in each of the nonsurviving dogs examined postmortem. Attempts are being made to devise a means of obliterating this dead space in the hope of eliminating the fibrin ring and embolic sequelae. These attempts, if successful, will be reported at a later date. In any case, even though the hazard of embolization is not large enough to contraindicate the use of the apical-aortic anastomosis procedure, the risk must be counted as a real one at the present time.

It was previously thought that the restriction of cardiac mobility by the insertion of a rigid prosthesis between apex and aorta might significantly hamper the mechanical activity of the ventricle. There are now reasons to believe that this is not a significant limitation. First, the heart affixed to the apical end of the prosthesis can easily rotate in a circle described by the rotation of the prosthesis around the long axis of the aorta. This has been demonstrated by rolling the open-chested dog with the prosthesis in place from the right lateral to the left lateral position. Second, the descent of the diaphragm and pericardium which lowers the heart in the chest is readily accomplished with only a slight change in the angle which the prosthesis makes with the thoracic aorta. Third, the apex of the heart can move to right or left somewhat since the aorta probably

yields a little under these circumstances. The experiments of Ferguson, Shadle and Gregg[18] suggest that this facet of the problem is not one of great importance. These investigators, seeking a chronic preparation in which they could conveniently make dye injections and measure the pressures in the left ventricle, prepared their dogs by preliminary thoracotomy during which the apex of the left ventricle was firmly sutured to the anterior chest wall. Circulatory compromise was not noted as a result thereof. Finally, and most convincingly, the chronic dogs carry the apical-aortic anastomotic prosthesis without overt evidence of limitation of cardiac performance.

The myocardium which carries an excessively high work load in the presence of a low coronary perfusion pressure may be presumed to have little or no compensatory reserve. In such an individual, even the brief introduction of a valvulotome into the stenosed aortic valve must be looked upon as hazardous. For, however momentarily, it intensifies the hydraulic and physiological derangements the procedure is aimed at alleviating. The apical-aortic anastomosis procedure outlined above does not either obstruct ventricular outflow or lower coronary perfusion pressure in the course of achieving the result. The intracardiac intervention is as brief as any currently-practiced cardiac surgical maneuver (30 to 60 seconds). While this is probably not of great importance while operating on the normal dog's heart, it is anticipated that this factor may be of importance in the more irritable, marginal, hypoxic myocardium of the patient with severe aortic stenosis. It is also an advantage not to have to subject the patient to the complicated and incompletely understood techniques of hypothermia.

It is to be emphasized that in the above procedure, the ascending aorta was occluded simply for the purpose of demonstrating that the cardiac output could be effectively directed through the apex. It would not, of course, be done as part of the therapeutic maneuver. However, occlusion of the outflow tract of the left ventricle proximal to the coronary ostia would, together with the apical-aortic anastomosis procedure, provide relief from aortic insufficiency as well as aortic stenosis. Attempts to accomplish this are under way. It is also within the realm of possibility that the anastomosis procedure may make possible the repair or resection of certain types of aortic aneurysms as well as lengthy aortic coarctations.

Lastly, the timely and detailed studies of Gorlin and his coworkers[2] have provided a sound basis for predicting the lumen size of a prosthesis which would provide a satisfactorily low outflow resistance in man. These workers found that major hydraulic obstruction was encountered when the cross-sectional area of the aortic valve fell to approximately 0.5 cm.^{2}, or below. The cross-sectional area of the prosthesis used in the above dog experiments was 0.95 cm.^{2}. Discounting the pressure drop due to the length of the prosthesis, the same sized tube would provide substantial relief in man, and this opinion is confirmed by the observation that it supported vigorous activity in a 35-Kg. dog. If the internal lumen were increased to a diameter of 14 mm., the cross-sectional area would be 1.54 cm.^{2} and the outside diameter would be only 15 mm. Its resistance would be physiologically negligible when used for this purpose.

It may be that performance of this procedure in the heart of a patient with severe aortic stenosis will bring with it certain technical and physiological difficulties not readily imitated in the experimental laboratory. Unless these difficulties prove insuperable, the above procedure may prove to be a reasonable means of alleviating aortic stenosis.

Addendum

Since submitting this article for publication two of the seven surviving dogs succumbed 66 and 76 days after operation. One death was from a mesenteric embolus and the other from thoracic hemorrhage, apparently from the ascending aorta near the nylon clip. The other five dogs, six to eight months after operation, are vigorous and apparently not limited in their activities.

Doctors Sarnoff and Case, now at the National Heart Institute, Bethesda, Md., are continuing with this procedure and after several modifications of the prosthesis and method,

have done another series. The results indicate that some of the previous difficulties have been eliminated. No tube-vessel junction erosion or embolic phenomena have been encountered in this group although it is too early to be certain that they will not occur.

From the historical point of view it is of interest that Jeger occluded the ascending aorta and established a bypass from left ventricle to thoracic aorta by means of a vein containing a valve and succeeded in keeping one such dog alive for four days.[20]

Summary

An effective means of by-passing the aortic valve has been described. The applicability of this to the treatment of aortic valvular disease was discussed.

Summario in Interlingua

Esseva elaborate un efficace methodo pro poner le valvula aortic in derivation. Le sanguine sinistroventricular exi via le apice per un tubo de lucite connectite con un modificate valvula Hufnagel e alora entra le aorta thoracic. In canes assi tractate le arco ascendente del aorta pote esser occludite complete- e permanentemente sin causar ulle disrangiamento apparente del circulation. Post le operation iste canes curreva, saltava, e natava, e non esseva facilemente distinguibile ab canes normal. Le integre manipulation ventricular es completate intra 30 a 60 secundas. Es discutite le applicabilitate de iste procedimento al alleviation de stenosis aortic in humanos.

Acknowledgment

The authors gratefully acknowledge the help of Dr. Wittenborg of the Children's Medical Center with the angiograms, of Drs. Erik Berglund and Hans Borst who assisted with several of the surgical procedures, of L. Charlotte Sarnoff, and also of Dr. Royce Simpson of the Angell Memorial Hospital who rendered valuable veterinary assistance. Codman-Shurtleff, Inc., Boston, were helpful in refining some of the instruments used.

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Dipaxin—2-Diphenylacetyl-1,3-Indandione; Clinical Evaluation of a New Anticoagulant

By JOHN B. FIELD, PH.D., M.D., MARTIN S. GOLDFARB, M.D., ARNOLD G. WARE, PH.D. AND GEORGE C. GRIFFITH, M.D.

In the course of development of new anticoagulants, an indandione derivative has been subjected to a clinical evaluation. The new agent is one of the most potent hypoprothrombinemic substance known but it is readily counteracted with vitamin K. The agent was administered to a large series of patients with thromboembolic diseases and control of anticoagulant therapy was observed to be simple, reproducible, with a good predictability of response as well as with absence of toxic phenomena and a low order of bleeding complications. It has been administered to 11 patients for ambulant anticoagulant care for periods up to 18 months with satisfactory results and it appears to be especially suitable for long-term maintenance therapy.

IN the treatment of thromboembolic diseases the use of anticoagulants has become an established modality. It is generally agreed that the popularity and application of this class of drugs would be increased if several disadvantages in the existing drugs could be overcome.[1-4] The ideal anticoagulant still awaited is one which (a) can be given orally, (b) has rapid anticoagulant effect, attaining therapeutic levels in minutes or hours and (c) almost as rapidly the anticoagulant effect can be nullified with return to normal coagulation either by withdrawal of the drug or use of a simple antidote; (d) permits therapeutic levels to be reliably maintained over long periods of time with need for only occasional laboratory determinations and (e) is inexpensive and nontoxic. The hypothetical agent would combine the best features of the two categories of anticoagulants now available, heparin and heparinoids, and the prothrombin depressants; but as yet no single substance incorporating these qualities has appeared.

The search, however, is progressing. Newer heparinoids appear to be unsuitable primarily because of uncontrollable side effects.[5-7] Several prothrombin depressants have been introduced since Dicumarol came first into use in 1942 but they are all coumarin or indandione derivatives and practically offer only minor differences from the action and effects of Dicumarol to recommend them. In the course of clinical evaluation of experimental anticoagulant drugs this laboratory has been studying a new indandione derivative, Dipaxin,* possessing some advantages which were mentioned in a preliminary note[4] and in several clinical reports.[8, 9] The present paper summarizes observations in about 200 subjects receiving the drug, some of whom received treatment for longer than one year.

METHODS

Prothrombin estimations were made by the diluted plasma technique developed by this laboratory involving a special heparin-oxalate collection fluid.[10] Results are recorded in per cent of a dried stable plasma standard which was adjusted to the mean of 20 normal individuals.

During the two years of study on the wards of the Los Angeles County General Hospital approximately 75 patients were selected for control single-dose studies. The acutely ill and those with hepatic and renal diseases and blood dyscrasias were omitted. The patients were unselected as to sex and age. The antidotal effect of vitamin K was studied on some of these subjects. A second group of 109 subjects received the drug as specific therapy for some thromboembolic disease.

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This study was supported by a grant from the Upjohn Company, Kalamazoo, Mich.

* A trademarked product furnished by Dr. H. F. Hailman, The Upjohn Company.

The following studies were conducted on each patient during the use of Dipaxin: frequent urine examinations, blood counts, liver function tests (cephalin flocculation, thymol turbidity, total protein and albumin-globulin ratio) and nonprotein nitrogen levels of plasma.

The drug was given orally in the form of 1 and 10 mg. tablets.

Results

Effect of Single Doses of Dipaxin

The plasma prothrombin levels were measured daily in patients given single doses of Dipaxin. These results are summarized in table 1. Patients receiving from 0.5 to 1.0 mg. of the anticoagulant exhibited no significant change from the initial level. The prothrombin of four of five patients given a dose of 2 mg. was slightly reduced and a hypoprothrombinemia was established in all of four patients given 4 mg. Dipaxin. Increasing doses of the indandione anticoagulant induced a more intense and longer-persisting hypoprothrombinemia. With a dose of 20 mg., prothrombin concentration fell to 55 per cent by the second day, remaining at that level until about the fifth day. A greater individual variability in response was observed than is evident in table 1 which records only the average of a number of subjects. Further, one individual in each of the groups given 15 or 20 mg. exhibited a moderate to almost complete resistance to the hypoprothrombinemic effect.

TABLE 1.—*Effect of a Single Dose of Dipaxin on Prothrombin Levels in Man*

Dose mg.	Control	Prothrombin (in %) Days								
		1*	2	3	4	5	6	7	8	9
0.5	120	123	110	125						
1	107	110	103							
2	122	111	105	113						
4	123	105	93	126						
6	129	113	103	103	130					
8	145	106	86	97	93	106				
10	116	85	78	85	85					
15	131	90	79	77	74	67	90	88	100	
20	121	93	55	55	59	71	72	79	84	83

Each line of figures is an average of results observed in four to eight patients.

* Actually represents the prothrombin level about 24 hours after drug rather than 24 hours, the drug usually being given at 6 p.m., thd blood sample withdrawn the following 8 a.m.

Effect of Vitamin K on Dipaxin Hypoprothrombinemia

In control subjects the degree of hypoprothrombinemia following a single dose of Dipaxin was either inhibited before its initiation or restored to normal by preparations of vitamin K. Seven patients were given 20 mg. of Dipaxin simultaneous with 150 mg. of a water-soluble vitamin K analogue, Synkayvite,* given intramuscularly. The vitamin K was given daily in the same dose until normal prothrombin levels were restored. A protocol of the data of one patient and a summary of a similar trial in seven patients is given in table 2. In subjects given the indandione anticoagulant over a longer period of time, 100 mg. vitamin K_1† given intravenously invariably reestablished normal prothrombin levels rapidly within 24 hours. Two illustrative protocols are included in table 2.

Use of Dipaxin as a Therapeutic Anticoagulant

Disease States Treated. The thromboembolic diseases and other states represented in the treated group are summarized in table 3.

Initial Therapy. Several different combinations of first and second day dosage were applied in order to achieve the most rapid and efficient prothrombin-reducing schedule. Ultimately it was observed that first-day dosage of from 20 to 30 mg. followed by 10 to 15 mg. the second day would induce an effective and usually therapeutic hypoprothrombinemia within 48 hours. In many cases at the option of the ward staff, heparin was also administered and some patients initially given Dicumarol were transferred to maintenance of hypoprothrombinemia with Dipaxin. In table 4 is indicated the time required to obtain

* A trademarked product of Abbott Laboratories, North Chicago, Illinois, which is 2-methyl-1,4-naphthohydroquinone diphosphoric ester tetra sodium salt.

† Mephyton, a trademarked product of Merck & Co., Rahway, New Jersey, which is 2-methyl-3-phytyl-1,4-naphthoquinone.

TABLE 2.—*Protocol of Effect of Synthetic Vitamin K and Vitamin K_1 on Hypoprothrombinemia Induced by Dipaxin*

Diagnosis	Control	Prothrombin (in %) Days																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Control	90	100	28	22	21	24	29	45	80	74	78	80	100					
(Patient A. W.)	20†																	
Control*	100	88	68	43	45	72	80	84	94	120								
(Patient A. W.)	20†																	
Control*	108	64	78	85	112													
(av. 7 patients)	20†																	
Thrombophlebitis	120	77	49	31	39	45	43	42	100									
	15†	10	4	4		6	4	‡										
Thrombophlebitis	140	82	50	54	39	36	43	39	44	—	32	21	24	60	43	33	90	140
	20†	10	5	5	3	3	5	4	4		4	2	0	6	4	3‡		

* Plus 150 mg. vitamin K daily (I.M.) (Synkayvite).

† Dipaxin in milligrams.

‡ 100 mg. vitamin K_1 (I.V.) (Mephyton).

prothrombin levels of 10 to 30 per cent in all patients initially given Dipaxin.

Maintenance Therapy. For maintenance therapy, in the average patient, it was found convenient to follow a sliding scale of dosages based on the prothrombin level observed on the day of therapy. This plan was applied successfully on a number of the wards of the hospital by the resident staff otherwise unfamiliar with the effects of Dipaxin. This schedule was helpful in maintaining prothrombin concentrations on most patients over long periods of time. Table 5 outlines the dosage plan.

Results. As the major criterion it is necessary to state the defined requirement of this laboratory for adequate therapeutic hypoprothrombinemia, and this is considered to be a prothrombin level of between 10 and 30 per cent. Upon this definition most of the following data are founded.

Table 6 gives the analysis of distribution of patients based on the total dosage of Dipaxin given and duration of maintenance of dosage.

As an index of the distribution of the dosage required by individual patients in order to maintain the desired prothrombin levels, table 7 is given.

The sum of the experience of this clinic with Dipaxin as an anticoagulant has been analyzed by the use of arbitrary standards in order to obtain an evaluation of its effectiveness in maintenance therapy. This has been accomplished by the following criteria: "excellent control"—after reduction of prothrombin time to therapeutic levels, four of every five prothrombin estimations were between 10 to 30 per cent during a full course of therapy; "good

TABLE 3.—*Disease States of Patients Treated With Dipaxin*

Myocardial infarction	72
Coronary insufficiency	18
Thrombophlebitis	15
Arteriosclerosis obliterans	2
Congestive heart failure	1
Postoperative mitral commissurotomy	1
Total	109

TABLE 4.—*Number of Days With Dipaxin Therapy Required to Reduce Prothrombin Time to 10–30% Level*

Days	Number of Patients
1	5
2	39
3	17
4	16
4+	8
Total	85*

* Some patients were not maintained on therapy long enough to establish this point, or had been on Dicumarol therapy before receiving Dipaxin.

TABLE 5.—*Dosage Scheme Determining Daily Dose of Dipaxin Administered for Maintenance Therapy**

Prothrombin Level Observed in Patients (in %)	Dosage Dipaxin Administered (mg.)
90–100	18
80–90	16
70–80	14
60–70	12
50–60	10
40–50	8
30–40	6
20–30	5
10–20	3
>10	0

* This plan has been found dependable in the average patient. Very obese individuals occasionally have required doses several times that indicated here.

TABLE 6.—*Summary of Therapeutic Experience with Dipaxin—Total Dosage and Therapy Days*

Total Accumulative Dose of Dipaxin (mg.)	Number of Patients	Number of Days Dipaxin Received	Number of Patients
10–50	36	1–10	37
50–100	38	10–20	38
100–150	16	20–30	14
150–200	4	30–40	7
200–300	0	40–50	1
300–400	5	50–100	3
500–600	3	100–150	3
600–900	2	150–200	4
1000–1500	3	450+	2
2500–4500	2		
Total	109		109

control"—at least three of five estimations were in the therapeutic range; "fair control"—at least two of five estimations were in the therapeutic range; "poor control"—only one of five estimations was in the therapeutic range; and "failures"—no estimations were within the therapeutic range. The results of applying these standards to all the patient data are given in table 8.

Untoward Results in Patients Receiving Dipaxin

It appeared that abnormal responses of any type were remarkably few. This occurred despite the relative unfamiliarity of some members of the resident staff arriving on service wards where Dipaxin was the only anticoagulant available. All individual untoward results which we observed follow:

1. Patient J. B. developed two episodes of bleeding: (a) Small ecchymoses appeared on the lower extremities during the first month. These subsided while on therapy.

(b) Microscopic hematuria associated with prothrombin less than 10 per cent developed in the fifth month of therapy. Drug discontinued and 100 mg. vitamin K_1 given and symptoms ceased immediately (fig. 1).

2. Patient E. T. developed occasional mild gingival bleeding from second to eighth month

TABLE 7.—*Average Daily Dose of Dipaxin Required to Maintain Therapeutic Hypoprothrombinemia*

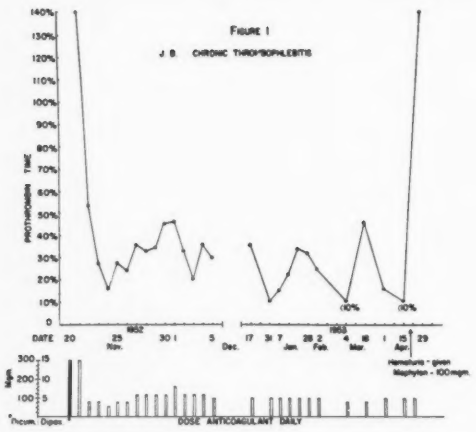
Daily Dose of Dipaxin (mg.)	Number of Patients
2	2
3	10
4	33
5	26
6	19
7	3
8	2
9	—
10	1
Total	96*

* Some patients were not maintained on therapy long enough to establish a specific dose.

TABLE 8.—*Effectiveness of Maintaining Anticoagulant Therapy With Dipaxin During Full Therapeutic Course*

Description of Control	Number of Patients
Excellent	51
Good	21
Fair	11
Poor	3
Failure	1
Course of therapy too short	22
Total	109

Definition of arbitrary standards: After reduction of prothrombin time to therapeutic level, degree of effectiveness is decided by the number of estimations of every five that the prothrombin level is between ten and thirty per cent. Excellent—4 out of 5; Good—3 out of 5; Fair—2 out of 5; Poor—1 out of 5; Failure—0 out of 5.



of therapy but only following brushing of teeth (fig. 2).

3. Patient P. R. Ten days after Dipaxin was started for myocardial infarction, while prothrombin level was 21 per cent, this patient had venous thrombosis of both lower extremities and left hand and expired.

4. Patient C. G. After four months on Dipaxin with frequent prothrombin levels less than 10 per cent, this patient failed to discontinue drug (3 mg. daily), as instructed, when prothrombin fell to less than 10 per cent, and after several days developed gross hematuria. Admitted to hospital, hematuria stopped several hours after 100 mg. vitamin K_1 intravenously and two units blood were given. Prothrombin level in 24 hours was 100 per cent. Patient had previously been known to be sensitive to Dicumarol.

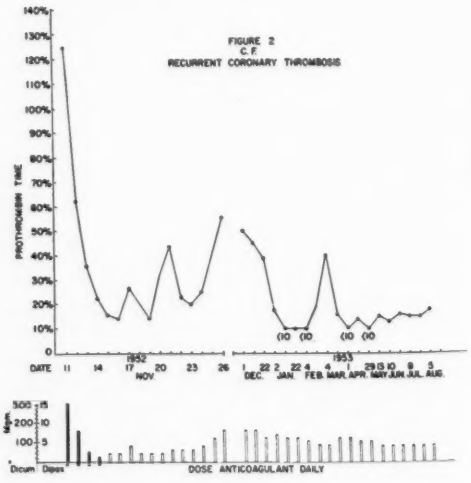
Ambulant Long-Term Maintenance Anticoagulant Therapy

There is a growing trend to utilize long term maintenance anticoagulant care as a prophylactic measure. In this category is frequently included patients with chronic recurring thrombophlebitis, valvular heart disease with recurrent embolization, second or more coronary thromboses and those with advanced coronary artery disease and incipient thrombosis. However, aside from the deterrent of risk of administering therapy, is the relative poor predictability and control with the prothrombin-depressing agents at hand.

With this in mind, on an ambulant basis it has been possible with Dipaxin to maintain excellent therapeutic hypoprothrombinemia for a period of three months or longer in a group of 11 patients. In fact, of the initial group, two patients remain on Dipaxin therapy about 18 months after its initiation at the time of this writing.

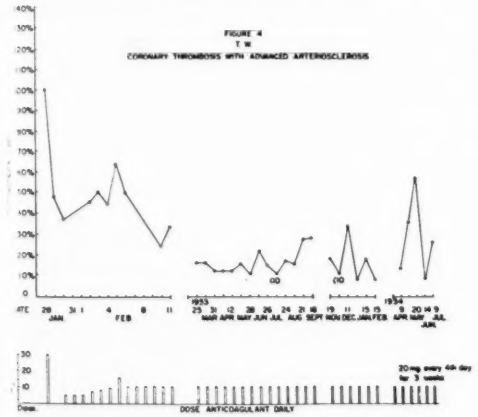
The disease states included representatives of most conditions given above. The patients were not only ward patients of the Los Angeles County Hospital but two were private patients whose therapy was begun and maintained at home. Although, as customary, with limited availability of prothrombin assays, estimations were done daily while the patients were hospitalized. At discharge, they were maintained on the daily dose of Dipaxin which appeared most suitable. Initially they were seen in the Clinic once weekly, subsequently once every two or even three weeks; when prothrombin assays were done, they were issued the drug.

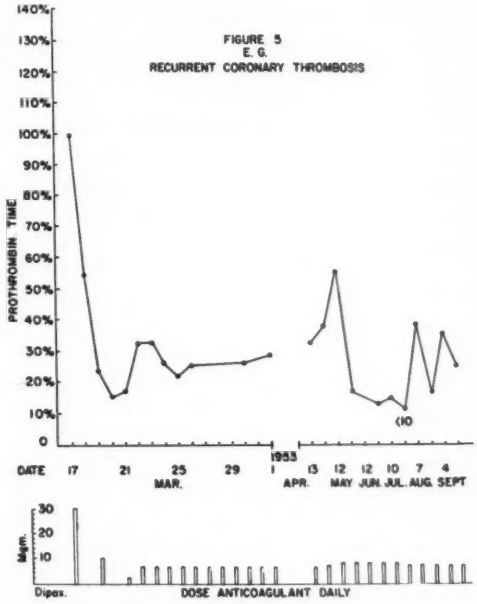
From time to time, blood and urine examinations were also done as a control measure. Only occasionally was it necessary to make some change in the established daily dose to keep the prothrombin level in the desired 10 to 30 per cent range. It was with considerable ease and apparent safety that this anticoagulant care was maintained on an ambulant basis. In only one instance was it necessary to



discontinue therapy because of an abnormal response. This was in a woman with recurrent thrombophlebitis and a history of ecchymosis and purpura over many years who, on Dipaxin therapy, manifested hematuria on one occasion when the prothrombin level was less than 10 per cent. Dipaxin was stopped and she was given 100 mg. vitamin K_1 intramuscularly; the hematuria ceased almost immediately and one week later a recheck prothrombin level was 140 per cent (figure 1).

In the following figures (figs. 2, 3, 4 and 5) are summarized the experiences of several additional patients who have been successfully maintained on Dipaxin for long periods of time.





Discussion

As has been indicated in a previous report,[4] Dipaxin is certainly one of the most potent hypoprothrombinemic agents known for man. However, simply that a smaller dose of drug is needed to achieve a similar effect, when compared with other drugs, is not, necessarily, a recommendation. In the detailed report given here it is indicated that Dipaxin has received extensive general clinical trial over a two-year period in patients on the wards and clinics of a general hospital (as well as in a number of private patients), with considerable satisfaction. It has, in general, been as effective, or more so, than other hypoprothrombinemic agents that we have used, although no direct comparison has been attempted at this time. It has proved to be uncomplicated to use, quite predictable in its response, reproducible in its dose-hypoprothrombinemia ratio in the individual patient, has safely been used over long periods in patients in whom only infrequent prothrombin estimations were done (two or three-week intervals), and has had a very low order of complicating manifestations requiring drug withdrawal. By comparison with other available and experimental anti-

coagulants heretofore used at this center, Dipaxin would appear to be the equal of, or more satisfactory than, others for general usage.

It appears that on a weight basis, Dipaxin is about 15 times more potent in man than Dicumarol, but in general its hypoprothrombinemia resembles closely that induced by Dicumarol. Using the initial dose schedule as outlined, 51 per cent of all patients had achieved a therapeutic hypoprothrombinemia in 48 hours, 72 per cent in 72 hours.

By the arbitrary standards given, 47 per cent of all treated patients had an excellent therapeutic control, an additional 20 per cent had good control and only 4 per cent had poor to bad control. There were no fatalities in the series of 109 treated patients (or of the total of about 200 patients who received Dipaxin) and no serious complications. Bleeding phenomena were surprisingly few, and only one patient (of the total of 109) who had developed hematuria required special attention. It had been demonstrated that vitamin K compounds (especially K_1) readily correct Dipaxin hypoprothrombinemia and again in this instance, 100 mg. of vitamin K_1 immediately halted the hematuria. Unlike other experience with another indandione compound, Hedulin, which has been reported to induce signs of renal toxicity,[11] no specific evidence of parenchymal damage to the kidney has appeared. No other outstanding toxic manifestation was observed; even in patients receiving the drug daily and continuously for periods of 6 to 18 months.

In a conference on therapy, Wright[3] has indicated that his objective of optimal therapeutic prothrombin activity for long-term anticoagulant therapy is to maintain the 25 to 50 per cent range. The standards used in this study with a relatively small group of patients receiving long-term Dipaxin therapy were somewhat more taxing since a lower range (10 to 30 per cent) was sought, and yet the control of prothrombin levels was accomplished with ease in almost all subjects even though the ambulant patient had estimations done only once every two or three weeks. In another report, Tullock and Wright[12] point out that in 227 patients who received coumarin anticoagulants for four weeks or more, there was one hemorrhagic death and 70 hemorrhagic episodes in 43 patients. In the 20 patients of this study who received Dipaxin for more than four weeks there were observed only two minor hemorrhagic experiences, an incidence far less than that experienced with the coumarin agents. Bay and his coworkers[5] have also recently reported on the use of Dicumarol in long-term therapy and they record an experience with a large number of minor, and occasionally massive, hemorrhagic tendencies. Despite use of weekly prothrombin determinations they felt that their control of therapy was relatively poor.

From the specific viewpoint of affording a safer and more predictable agent for long-term anticoagulant care, it would appear that Dipaxin merits further clinical trial.

Conclusions

1. A new anticoagulant, Dipaxin (diphenylacetyl-1,3-indandione), has been studied in 200 human subjects. It has effectively induced a therapeutic hypoprothrombinemia in 48 to 72 hours and with repeated doses has sustained such hypoprothrombinemia in some patients for 18 months.

2. On a weight basis, it appears to be the most potent hypoprothrombinemic agent known. Its anticoagulant properties are readily overcome with vitamin K, the natural vitamin being more effective than the synthetic.

3. A group of 109 patients with thromboembolic indications received Dipaxin as specific therapy and 11 patients were maintained on ambulant anticoagulant care from 3 to 18 months. Control of anticoagulant therapy was impressive for its relative ease, reproducibility and predictability of response, absence of toxic phenomena and extremely low order of bleeding complications.

4. The agent appeared to be especially suitable for long-term maintenance control where prothrombin estimations could be made only at intervals of several weeks.

Conclusiones in Interlingua

1. Esseva studiate in 200 humanos le nove anticoagulante Dipaxina (diphenylacetyl-1,3-

indandiona). Illo ha efficacemente producite un hypoprothrombinemia therapeutic intra 48 a 72 horas, e con dosages repetite susteneva tal hypoprothrombinemia in alicun patientes durante 18 horas.

2. Comparate peso pro peso, Dipaxina pare esser le plus potente agente hypoprothrombinemic nunc cognoscite. Su virtutes anticoagulante es prestemente neutralisate per vitamina K, e in isto le forma natural del vitamina es plus efficace que le forma synthetic.

3. Un gruppo de 109 patientes con indicationes thromboembolic recipeva Dipaxina como therapia specific. Dece-un patientes lo recipeva durante 3 a 18 menses de regime ambulante. Le curso therapeutic esseva impressive per le relative facilitate de su maneamento, per le possibilitate de reproducer e predicer le responsas, per le absentia de phenomenos toxic, e le extreme infrequentia de complicationes sanguinatori.

4. Le agente pareva specialmente utile in casos requirente le mantenentia de controlo a longe durantia ubi estimationes de prothrombina poteva esser facite solmente a intervallos de plure septimanas.

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Observations on the Hyponatremia following Mitral Valvulotomy

By ALLAN V. N. GOODYER, M.D. AND WILLIAM W. L. GLENN, M.D.

Thirty-seven patients subjected to mitral valvulotomy were studied before and after operation with regard to the incidence, extent, and mechanism of postoperative hyponatremia. Balances of water, sodium, and chloride were carried out on 27 patients. The serum sodium fell below 131 mEq. per liter in 16 cases in the immediate postoperative period, the serum chloride fell below 99 mEq. per liter in all cases but one and below 90 mEq. per liter in 11 cases. The small negative balances of sodium and chloride were inadequate, by themselves, to account for the observed hyponatremia in any case. Appreciable (over 100 mEq.) intracellular shifts of sodium (using the chloride space as a reference) were associated with hyponatremia in only three cases. The retention of water during the immediate postoperative period (allowing for insensible losses) was enough to explain the observed hyponatremia in all but three cases, although the level of fluid *intake* was not well correlated with the occurrence of hyponatremia. These results indicate the presence of an unusually prolonged antidiuretic stimulus in these patients, the etiology of which remains uncertain. Except in a few cases it is unnecessary to correct the hyponatremia with hypertonic salt, since it is usually a transient, limited, and essentially asymptomatic phenomenon.

HYPONATREMIA following major operative procedures has been related to sodium depletion (usually via drainage from the gastrointestinal tract),[1] or to "excessive" administration of salt-free fluids in the postoperative period.[2] When the intake of fluid is set at 4000 cc. per day in patients subjected to gastrectomy, the serum sodium is reduced slightly for only about 24 hours.[3] When only 2500 cc. per day is given, hyponatremia following major thoracotomy in patients without heart disease is largely avoided.[4] In patients subjected to mitral valvulotomy, however, hyponatremia has been observed by us under conditions where neither sodium depletion nor the excessive administration of water seemed to apply.

Such patients were, therefore, studied by the balance technique, described below, in an effort to discover:

(1) The incidence, severity and persistence of hyponatremia, and the need for its treatment.

(2) The features of their rheumatic heart disease which might be implicated in the development of hyponatremia.

(3) The possible rôle of dilution of the body electrolytes by fluids administered in seemingly moderate quantities.

(4) The possible rôle of an intracellular shift of sodium in explaining extracellular hyponatremia.

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This work was supported by a grant from the American Heart Association to Dr. Goodyer now an established Investigator.

During the period of this study, Dr. Goodyer was a Markle Scholar in Medical Science at Yale.

PROCEDURE AND METHODS

Thirty-four patients of a total group of 115 subjected to mitral valvulotomy during the three year period from June, 1951 to June, 1954 were chosen for the present study. The clinical data bearing on the severity and type of their rheumatic cardiovascular disease are summarized in table 1. Changes of the serum electrolytes were closely followed in all patients. In 24 of the 34 cases, balances of sodium and water were measured during the postoperative period as indicated below. Each patient was put on a low-sodium diet of known content (usually 200 mg.). Two patients (cases 3 and 21) received extra sodium chloride, in addition to the salt-free diet, in the immediate postoperative period. Urine and chest drainage were collected in consecutive 24-hour aliquots. Stools were not studied, but in the postoperative period covered by this study were infrequent. Body weights were obtained before operation but could not be obtained in the postoperative

TABLE 1.—*Clinical Features of Patients Subjected to Mitral Valvulotomy*

Patient			Pre-op. Status					Post-op. Status								
														Residual Valve Abn.[i]		
No.	Age	Sex	Class[a]	CHF[b]	NPN[c]	PSP[c]	BSP[c]	Hypo-natr.[d]	NPN	Narc. Units[e]	Hypo-tens N[f]	Arrhy-thmia[g]	Rheu. active[h]	M.S.	M.I.	A.
1	38	F	2		29			1	28	9D		+		+		
2	46	F	4	+	31			2	31	4D	op.		+			+
3	46	M	4F	+	36		19		65					+	+	
4	28	F	4	+	27	59			35	8D		+				
5	30	F	3F		31			j		8D	++	+	+		++	+
6	38	M	3F		37	55				10D					+	
7	46	F	3F		34				40	9D	+				+	
8	51	F	4F	+	36		25		52		op.					+
9	37	F	4F	+			21	2[j]		7D					++	
10	21	F	2		24			1		9D						
11	54	F	2F		35	60				2D					+	
12	42	F	3F		28		5			8D			P			
13	49	F	3		28	55		2		7M	op.	+		+		
14	46	M	3F		33	50		1		10D			+PA	+	+	+
15	54	F	3	+	33			1		9D		+				
16	41	M	3F		36					6D			P			+
17	35	F	3	+	30	70		1			op.	+				
18	30	F	3	+	27	85	18		36	8D		+				+
19	42	F	3F	+	25	45	4		33	8D				+		
20	28	F	3		34	60	9	1	26	7D		+				
21	24	M	3		28	65	3	1[j]	84	13DM					+	+
22	25	F	3F		33	55	2	1	29	12D	+				++	
23	48	F	2F		33	40	1		31	4D						
24	43	F	3F		35	90	20		35	3D						
25	42	F	3		33	50	5	1	30	3D						
26	55	M	3F		33	40	3	1		13D	+			+	+	
27	38	M	2		30	45	3	2	70	13M		+	P			+
28	40	F	2		33	61	5	2	36	3M	+		+P			
29	41	F	3F		40	45	12	1	36	8M	+				+	+
30	35	F	3	+	32	53	7			15D		+		+		
31	48	F	3F		38		13	1		9D			+P			+
32	31	F	3		33	45	13		30	13D	+		+P			
33	41	F	4F	+	43	20	29	1		4M			+			
34	51	F	4F	+	38			1	52	2M	+			+		

[a] Classification of American Heart Association. F indicates chronic auricular fibrillation.

[b] CHF = Congestive Heart Failure (including peripheral edema) at some time in the year preceding operation. This had been controlled insofar as possible pre-op. by digitalis, mercurials, and SF diet.

[c] NPN = Blood nonprotein nitrogen, mg.%; PSP = Phenosulfonphthalein, % of injected dose excreted in two hours; BSP = Bromsulphalein, % retention in blood 45 mins. after injection of 5 mg./kg.

[d] Hyponatremia post-op. (within period of balance study) *1* designates value 130 mEq./L. or less, *2* designates value 125 mEq./L. or less.

[e] "Narcotic Units" (1 unit = 100 mg. Demerol = 10 mg. morphine), given during the first three days post-op.

[f] Hypotension, defined as persistent systolic pressure below 90 mm.Hg during operation (op.), or below 100 mm.Hg for at least 12 hours post-op. if Levophed was not infused.

[g] Sudden new arrhythmia causing tachycardia which has not been present pre-op. (usually auricular fibrillation or flutter).

[h] "Rheumatic activity" as indicated by elevated ASL titer (+), unusually prolonged or recurrent pleuritis and pericarditis (P), or acute arthritis (A).

[i] Residual valve abnormality: *M.S.*, + indicates that split obtained in valve was good, but not excellent (to 2 fingers or less); M.I., + and ++ indicates mild-to-moderate and marked mitral insufficiency resp.; A+ indicates definite, but not marked, aortic stenosis or insufficiency as a complicating valvular abnormality.

[j] Indicates post-op. fatality (case no. 5 in shock; cases nos. 9 and 21 in congestive failure).

TABLE 2.—*Serum Electrolytes in Patients Subjected to Mitral Valvulotomy*

Patient No.	Period A*					Period B*					Per. A+B*		Estimated Change in	
	Time, days	Inital serum value†		Change in serum‡		Time. days	Initial serum value†		Change in serum		Change in serum		Serum Na§	
		Na	Cl	Na	Cl		Na	Cl	Na	Cl	Na	Cl	Per. A	Per. A+B
		mEq./L.		mEq./L.			mEq./L.		mEq./L.		mEq./L		mEq./L.	mEq./L.
1	3	137	*94.7*	−7	*0*	1	131	*87.7*	+1	−6	−13	−6	−5	−6‖
2	2	139	*97.0*	*−16*	*−8*	2	140	*92.8*	+17	+4	−12	−4	−14	−7‖
3	2	137	*97.0*	−3	*−2*	2	136	*99.0*	+2	+4	+1	+2	−6	−5
4	1	137	*95.8*	−3	*−5*	3	134	*85.0*	0	−6	−9	−11	−4	−9
5	2	140	103	−9	*−9*	—	—	—	—	—	—	—	−10	—
6	1	140	*97.7*	−7	*−10*	2	137	*86.5*	+4	−1	−8	−11	−4	−7
7	3	131	*96.7*	+9	*−5*	2	137	—	−3	—	—	—	−12	—
8	1	138	*98.0*	+2	*0*	2	137	*87.6*	−3	−10	−8	−10	−4	−7
9	2	138	*92.2*	−7	*−4*	3	*116*	*81.2*	−15	−6	−13	−10	−6	−24
10	1	137	102	*−9*	*−9*	3	136	105	+8	+12	+3	+3	−7	−4
11	1	143	*93.2*	−6	*+2*	—	—	—	—	—	—	—	−4	—
12	3	146	99.5	−11	*−8*	—	—	—	—	—	—	—	−1‖	—
13	2	139	100	*−14*	*−14*	2	133	*94.0*	+8	+8	−6	−6	−8‖	−14
14	2	137	102	−2	*−13*	2	*126*	*83.0*	−9	−6	−11	−19	−9	−14
15	2	139	*90.5*	*−9*	*−6*	2	136	—	+6	—	—	—	−7	—
16	3	140	*95.5*	−4	*−11*	—	—	—	—	—	—	—	−16	—
17	1	142	104	*−13*	*−9*	5	139	*96.7*	+10	+2	—	—	−6‖	—
18	2.5	132	100	−1	*−2*	—	—	—	—	—	—	—	−6	—
19	1	137	100	−3	*−4*	4	137	*93*	+3	−3	0	−7	−2	−9
20	1	136	102	*−6*	*−7*	3	133	*92*	+3	−3	−3	−10	−3	+1
21	1	139	103	*−12*	−4	3	*128*	*90*	+1	−9	−11	−13	−4‖	−11
22	1	136	102	*−6*	*−7*	5	*127*	*85*	−3	−10	−9	−17	−6	−4‖
23	1	147	106	−12	*−8*	3	138	*93*	+3	−5	−9	−13	−4‖	−7
24	1	141	101	−2	*−6*	3	133	*90*	−6	−5	−8	−11	−3	−1‖
25	2	141	—	*−11*	—	—	—	—	—	—				
26	1	138	102	−5	−10	3	*128*	*91.2*	−4	0				
27	2	142	*96.0*	*−17*	*−12*	5	*123*	*75.0*	−2	−9				
28	2	135	101	*−10*	*−15*	—	—	—	—	—				
29	1	134	*98.2*	*−8*	*−11*	2	*128*	*85.5*	+2	−3				
30	1	137	103	−2	*−8*	3	134	*88.5*	−1	−6				
31	1	140	101	*−10*	*−10*	3	133	*89.2*	−3	−5				
32	1	141	101	−5	−7	2	143	*93.5*	+7	0				
33	2	134	107	*−4*	*−12*	—	—	—	—	—				
34	2	139	105	*−10*	*−15*	4	138	100	+9	+10				

* Period A begins on the morning before operation; period B directly follows period A.

† Hyponatremia (serum sodium less than 131 mEq./L.) and hypochloremia (serum chloride less than 99 mEq./L.) are indicated by italicized values.

‡ Italicized values indicate hyponatremia and/or hypochloremia occurring at the end of Period A (beginning of period B).

§ Estimated change in the serum which would have been caused by the calculated balances of water and sodium, in the absence of an intracellular shift of sodium (see *Methods* for the calculations and assumptions involved). Parallels‖ indicate estimated decreases in the serum sodium which were not adequate to account for the observed decreases.

periods with enough regularity to be used in estimating water balances. Balance data were obtained in two periods in each patient: *Period A*, beginning on the morning of operation, and of 1 to 3 days duration; *period B*, following period A, and of 1 to 3 days duration. Blood for chemical analyses was taken at the beginning and end of each of these balance periods. All patients had been digitalized before operation, and were treated with antibiotics during the postoperative period.

Electrolytes, nonprotein nitrogen, and bicarbonate in the blood, and electrolytes in the urine were determined by standard methods, including flame photometry.

TABLE 3.—*Estimated Balances of Water and Electrolytes in Patients Subjected to Mitral Valvulotomy**

Patient No.	Initial Body Weight kilos†	Overall Balance‡		Extracellular Balance‡			Intracellular Balance‡		Urine Loss	
		Na mEq.	H_2O liters	Na mEq.	Cl mEq.	Vol. liters	Na mEq.	Vol. liters	Na mEq.	K mEq.
Period A										
1§	73.6	−13	+2.0	−162	−47	−0.4	+149	+2.4	39	153
2§	40.0	−73	+2.5	−302	−190	−1.4	+229	+3.9	61	69
3	68.2	+171	+3.4	+230	+165	+2.0	−59	+1.4	1	48
4	54.5	−22	+1.1	+4	−27	+0.3	−26	+0.8	2	22
5	53.7	−97	+2.1	−215	−109	−0.1	+118	+2.2	19	45
6	76.2	−12	+1.5	+50	−47	+1.2	−62	+0.3	47	81
7	65.0	−11	+4.4	+145	−50	+0.2	−156	+4.2	11	65
8	53.6	−24	+0.8	−26	−27	−0.3	+2	+1.1	10	25
9	51.3	−51	+1.3	−77	−54	+0.1	+26	+1.2	16	
10§	52.8	−7	+2.0	+21	−13	+0.9	−28	+1.1	7	37
11	54.5	−34	+0.7	−158	−44	−0.7	+124	+1.4	2	18
12	64.5	−90	−0.3	−128	−103	+0.1	+38	−0.4	41	99
13§	59.1	−142	+1.3	−165	−169	0	+23	+1.3	38	94
14	69.0	−175	+1.9	+55	−134	+0.6	−230	+1.3	34	73
15§	56.5	−52	+1.6	−75	−48	+0.2	+23	+1.4	18	67
16	55.8	−6	+5.0	−166	−195	−1.0	+160	+6.0	13	137
17§	47.2	−53	+1.0	−90	−63	+0.3	+37	+0.7	22	43
18	58.2	+23	+2.4	−148	−104	−0.2	+171	+2.6	4	81
19	61.8	−114	+0.3	−170	−146	−1.0	+36	+1.3	11	116
20§	67.2	−7	+1.1	+51	−13	+1.0	−58	0	7	28
21§	70.0	−81	+1.0	−236	−109	−0.6	+155	+1.6	2	33
22§	39.1	−19	+1.2	−100	−95	−0.4	+81	+1.6	1	39
23	59.6	−21	+1.2	−35	−24	+0.8	+14	+0.4	21	24
24	54.1	−3	+0.9	+100	−7	+1.0	−103	−0.1	3	27
Period B										
1	75.6	+8	+0.4	+150	−4	+1.0	−142	−0.6	0	40
2	42.5	+4	−1.9	−63	−89	−1.2	+67	−0.7	2	33
3	71.5	−2	−0.2	−160	−79	−1.4	+158	+1.2	2	84
4	55.6	−12	+1.3	+24	−54	+0.2	−36	+1.1	2	54
6	77.7	−16	+1.0	−42	−86	−0.8	+26	+1.8	9	83
8	54.4	0	+0.9	+74	−45	+0.8	−74	+0.1	2	70
9	52.6	+21	+6.4	−81	−15	+0.4	+102	+6.0	2	40
10§	54.8	−32	−1.2	−104	−21	−1.5	+72	+0.3	27	67
13	60.4	+41	+2.4	−29	+8	−0.9	+70	+3.3	0	45
14§	70.9	−14	+1.7	+48	+34	+1.4	−62	+0.3	8	76
19	62.1	−23	+2.3	+45	−23	+0.1	−68	+1.2	2	87
20	68.3	−10	−1.9	+58	−31	0	−68	−1.8	4	62
21§	71.0	+262	+5.4	+505	+219	+3.9	−243	+1.5	3	193
22§	40.3	−8	−0.6	+3	−57	+0.2	−11	−0.8	2	86
23	60.8	−72	+0.6	−5	−84	−0.3	−67	+0.9	4	101
24	55.0	−7	−0.8	−10	−27	+0.8	+3	−1.6	10	73

* Values are for the entire balance periods, the durations of which are indicated for each patient in table 2. Section signs (§) indicate patients who were hyponatremic at the end of the corresponding balance period.

† Body weight at beginning of period A. Body weight at beginning of period B taken as body weight at beginning of period A plus small balance of water during period A.

‡ See *Methods* for calculations of these values.

Calculations of changes in the extracellular and intracellular electrolytes were made according to formulae previously presented.[5] The assumptions were made that chloride remained "extracellular" and that extracellular fluid volume in each patient at the beginning of *period A* was 20 per cent of the body weight. Corrections for the Donnan equilibrium and for serum water were omitted because of the negligible influence of such corrections on the date presented in tables 2 and 3. Water balance was estimated in each patient by careful measurement of intake and output during and after the operation, correction being made for an assumed insensible loss of 1000 cc. per day. This value, being somewhat high, partly allows for unmeasured losses of water through sweating during and after operation, some of which were also offset by unmeasured retention of fluid used for irrigation purposes during operation. Losses of blood during operation were approximately balanced by blood replacement and have not been included in these calculations.

In view of the above assumptions, the estimates of water balances and changes of intracellular water were only gross approximations. However, they provided (in conjunction with the much more accurate measurements of the balances of sodium) the basis for evaluating the *possibility* that retention of water might explain the decreases in the serum sodium observed in *periods A*. The "estimated changes in the serum sodium", table 2, were calculated for each balance period according to the following:

$$\left(\begin{array}{c}\text{Estimated change}\\ \text{in serum [Na]}\end{array}\right) = \frac{b\,Na}{0.7\ B.Wt.} - \left(\frac{b\,H_2O}{0.7\ B.Wt. + b\ H_2O} \times [Na]_s\right)$$

where:

bNa is the external balance of sodium.

$B.Wt.$ is the body weight at the beginning of the balance period.

bH_2O is the balance of water.

$[Na]_s$ is the concentration of the serum sodium at the beginning of the balance period.

Assumptions made in the use of this formula are (1) that $b\mathrm{H_2O}$ is accurate; (2) that $0.7\ B.Wt.$ is the total body water; (3) that intracellular and extracellular osmolarity are the same; (4) that there is no activation or inactivation of cellular or extracellular base during the balance period. The effects on this calculation of losses of sweat in excess of those allowed for in the values for bNa and bH_2O are discussed below.

Results

Serum Electrolytes

Changes in the serum electrolytes (table 2) were measured in 37 cases. The normal values for the serum sodium and chloride, for this laboratory, are 131 to 144 mEq. per liter, and 99 to 107 mEq. per liter, respectively. On this basis, the initial serum sodium was normal in all (37) cases, whereas the initial serum chloride was subnormal in about one-third of the cases (table 1). In the period during and following the valvulotomy (period A), the serum sodium decreased more than 4 mEq. per liter in 23 cases (average change, 37 cases, -7 ± 5 mEq. per liter); the serum chloride decreased more than 4 mEq. per liter in 22 cases (average change, 36 cases, -7 ± 4 mEq. per liter). *Hyponatremia* (values below 131 mEq. per liter) was present at the end of period A in 16 cases (values 125 mEq. per liter or below, in only six cases), *hypochloremia* (values below 99 mEq. per liter) was present in all cases but one (case 21), (values 90 mEq. per liter or below in 11 cases). The addition of 172 mEq. of sodium to the intake of one patient (case 3) in the immediate postoperative period may have limited the fall in the serum sodium in this case. There were variable small changes in the serum "total carbon dioxide" and potassium (averages, all cases, -1 ± 4 mEq. per liter and $+0.2 \pm 0.4$ mEq. per liter, respectively). The limited changes in the serum potassium were in contrast to the marked elevations reported by Wilson and coworkers under similar circumstances.[6]

During the recovery period (period B, see Procedure), the serum sodium returned to normal without saline therapy in all but four of the cases (cases 21, 22, 27 and 29) in which hyponatremia had developed during period A. In case 21, hyponatremia progressed in spite of the additional administration of 295 mEq. of sodium in three days. In three other cases (cases 9, 14 and 26) hyponatremia appeared for the first time. The serum sodium ultimately returned (spontaneously) to normal in all patients but two (cases 9 and 21) whose postoperative course was characterized by progressive heart failure. In these patients, saline therapy and other measures were of no permanent avail in correcting the severe hyponatremia.

Hypochloremia persisted throughout period B in all but two cases (cases 10 and 34), whereas

changes in the serum "total carbon dioxide" and potassium were minimal and variable (averages, 15 cases, $+1 \pm 2.5$ mEq. per liter and $+0.2 \pm 0.6$ mEq. per liter, respectively).

Only two patients (cases 9 and 21) had symptoms clearly referable to hyponatremia or hypochloremia. Neither alkalosis nor hypokalemia was observed in any case.

Extra- and Intra-cellular Electrolytes

Changes in the extra- and intracellular electrolytes were estimated in 27 patients (see table 3, and Methods), under the basic assumption that chloride remained extracellular. Because the prescribed dietary intake of sodium and chloride was minimal (except in cases 3 and 21) the overall balances of these ions were in most cases negative. Extracellular contents of chloride therefore declined during periods A and B in all but four cases (cases 3, 13, 14 and 21); extracellular content of sodium declined more variably (in about three-fourths of the cases). The negative balances of sodium were inadequate, by themselves, to account for any of the observed cases of hyponatremia. Intracellular balances of sodium varied inversely with the extracellular balances. However, the apparent intracellular shifts of sodium during period A were appreciable (over 100 mEq.) in only 7 of the 27 cases studied, only three of the seven (cases 1, 2 and 21) being cases of hyponatremia.

Estimations of Fluid Balance (Table 3)

The overall balances of water (Table 3) were positive during period A in all cases but one (case 12). Whereas changes in extracellular volume were variable, intracellular volume (as roughly calculated in the manner indicated under *Methods*), increased during period A in all but cases 12, 20 and 24 (more than 1 liter in 17 of the 27 cases studied). This evidence of water retention is supported by the observation of Wilson and associates[6] that patients subjected to valvulotomy and given fluids in amounts similar to those given the patients of this report *gained weight* during the operative and immediate postoperative period.

The calculated changes in the serum sodium which might have been expected, on the basis of the observations and estimates of sodium and water balance in each patient, are listed in table 2 (see *Methods* for calculations). The *calculated* decreases in the serum sodium were sufficient (within 4 mEq. per liter) to explain the *observed* decreases in all but five cases during period A (cases 12, 13, 17, 21 and 23), and in all but four cases (cases 1, 2, 22 and 24) during both balance periods together (A and B). Only four cases of hyponatremia (cases 13, 17, 21 and 22) at the end of periods *A* or *A and B* were unexplained by these calculations of the effects of water retention.

The average daily intake of water of those patients who developed hyponatremia is contrasted with the average intake of those patients who maintained a normal serum sodium in the following table:

Serum Sodium at End of Period	Average Water Intake per Day	
	Period A	Period B
Below normal	2.9 liters (9 pts.) (range, 2.4–3.7 L.)	2.8 liters (4 pts.) (range 2.0–3.3 L.)
Normal	2.5 liters (15 pts.) (range 1.9–3.2 L.)	2.5 liters (13 pts.) (range 1.9–3.1 L.)

Although the mean values would suggest a relation between hyponatremia and larger intakes of water, the *ranges* of values in each group invalidate the small differences in the *mean* values. Hyponatremia in these patients was not well correlated with "excessive" *intake* of water in the postoperative period, the positive water balances being due primarily to excessive *retention* of water (i.e., oliguria).

Sweat Losses

Although losses of water and sodium via sweating have been partly covered in the above calculations by the values for bNa and H_2O (see *Methods*), it is possible that sweating may have been underestimated. During period A, the unmeasured *extra* loss of 500 cc. of sweat containing 20 mEq. of sodium chloride would have increased the values for the intracellular balance of sodium, in cases 1 through

27, by only about 10 mEq., and would have added *no* cases in which the change in serum sodium could *not* have been explained by the overall balances of water and sodium, in the absence of an intracellular shift of sodium. However, the unaccounted loss of an *extra liter* of sweat in each case would have added three cases of hyponatremia which could not have been explained by the retention of water. Such sweating was not clinically evident in these cases.

Urinary Electrolytes

Urinary loss of sodium and chloride was minimal in all cases during both balance periods. Urinary loss of potassium was more pronounced, particularly during period B. This was not necessarily of cellular origin, since dietary intake may have matched the urinary loss.

Discussion

The above data indicate a high incidence of hyponatremia immediately following mitral valvulotomy. In some instances this was of moderately severe degree, but in only two patients (cases 9 and 21) did it introduce the ominous syndrome of progressive hyponatremia and anasarca characteristic of relentless, preterminal congestive heart failure. In all other patients studied here, the hyponatremia was self-limited, and essentially asymptomatic. Mental confusion was noted in several patients, but was not clearly related to hyponatremia in view of other possible causes, such as sedation. Similar observations have been made in a recent report by Wilson and coworkers.[6]

The data of tables 2 and 3 would suggest that the mechanism of the observed hyponatremia in most cases involved dilution by water retained in unusual quantity during the postoperative period, rather than sodium depletion or a shift of sodium from the extracellular water into the cells (or into bone or connective tissue). Transient retention of water, associated with oliguria, is characteristic of the period immediately following major surgery,[7] although it is not usually sufficient to cause prolonged hyponatremia if water intake is moderate.[3, 4] However, the possibility of a more consistent shift of sodium into cells in the present experiments cannot be *entirely* eliminated, because the assumption used in estimating this possibility (see *Methods*), namely that the chloride space accurately reflects changes in the extracellular water, may be open to some question. A shift of chloride into cells, connective tissue or bone in any case would have increased correspondingly the calculated shift of sodium into the same areas. Nevertheless, recent studies of the use of chloride, potassium thiocyanate and inulin for measuring the extracellular phase of tissues[8] indicate that the chloride space may at present be the best available measure of the volume of the extracellular fluid.

Whichever mechanism may have been involved in each case in the initiation of hyponatremia, the operation of an abnormal antidiuretic (water) stimulus was implicit in the observation that the serum sodium remained low, occasionally for as long as a week or more, in the absence of salt depletion or uremia. The normal physiologic response to a fall in the osmolarity of the body fluids is the inhibition of the secretion of antidiuretic hormone by the posterior pituitary, as a result of which the reabsorption of water by the renal tubules is decreased. The consequent diuresis restores internal osmolarity to normal. This regulatory mechanism may fail under a variety of circumstances characterized by excessive stimulation of the posterior pituitary (or possibly by the appearance of antidiuretic hormone-like substances from other sites or by a primary change in cellular osmolarity).[9] In particular, retention of water has been noted with disturbances of adrenal function and with general circulatory impairment, either of which might have been variably present immediately following mitral valvulotomy. It was of interest, therefore, to correlate the occurrence of hyponatremia in these patients with those clinical features which tended to affect adversely the postoperative circulatory status and which might therefore have been expected to favor water retention (table 1). Except cases 10, 25 and 31, every case of hyponatremia presented one or more of the following factors: prior congestive

failure; prolonged postoperative hypotension; disturbing new arrhythmia; overt rheumatic activity (arthritis); or more than the usual residual valvular abnormality. However, each of these factors was also present in one or more of the cases without hyponatremia. Therefore, in the absence of some more quantitative estimate of the degree of postoperative circulatory impairment, no clear distinction can be made on this basis between those patients who developed hyponatremia and those who did not. Of particular interest was the lack of correlation of hyponatremia with the development of the "postvalvulotomy syndrome" (consisting of cough, fever, pleuritis and/or pericarditis)—designated by *P* in table 1. The amounts and effects of sedative medications which have been implicated in postoperative water retention[10] were also no greater in the cases with hyponatremia than in those without. The antidiuretic effects of the operative anesthesia, itself, are known to last only a few hours.[10]

A few patients (cases 13, 17 and 21) may be expected to develop hyponatremia which cannot be explained by the retention of water.[6] It is our experience that it is unnecessary in most cases to attempt to correct this hyponatremia, since it is almost invariably a transient, limited and essentially asymptomatic phenomenon. Whether saline therapy would be *detrimental* cannot be decided from our data. In an occasional patient, the progression or persistence of hyponatremia warrants the administration of *hypertonic* saline, in an effort to improve the circulatory status. Such therapy is likely to be quite effective in the case of hyponatremia due to unusual salt depletion[6] (not observed in this series), but may be expected to be much less or not at all effective in the case of the ominous progressive hyponatremia associated (as in cases 9 and 21) with edema and increasing heart failure.

Summary

Thirty-seven patients subjected to mitral valvulotomy were studied before and after operation with regard to the incidence, extent, and mechanism of postoperative hyponatremia. Balances of water, sodium, and chloride were carried out on 27 patients. The serum sodium fell below 131 mEq. per liter in 16 cases in the immediate postoperative period, the serum chloride fell below 99 mEq. per liter in all cases but one and below 90 mEq. per liter in 11 cases. The small negative balances of sodium and chloride were inadequate, by themselves, to account for the observed hyponatremia in any case. Appreciable (over 100 mEq.) intracellular shifts of sodium (using the chloride space as a reference) were associated with hyponatremia in only three cases. The retention of water during the immediate postoperative period (allowing for insensible losses) was enough to explain the observed hyponatremia in all but three cases, although the level of fluid *intake* was not well correlated with the occurrence of hyponatremia.

The conclusion that hyponatremia was due in most cases to water retention is valid only if certain reasonable assumptions are allowed: (a) sodium losses in sweat were no greater than surmised, (b) chloride remained extracellular, (c) cellular osmolarity did not decrease.

The results indicate the presence of an unusually prolonged antidiuretic stimulus in these patients, the etiology of which remains uncertain. Except in a few cases it is unnecessary to correct the hyponatremia with hypertonic salt, since it is usually a transient, limited, and essentially asymptomatic phenomenon.

Summario in Interlingua

In 37 casos de valvulotomia mitral datos pre- e postoperative esseva usate in un studio del frequentia, del extension, e del mechanismo de hyponatremia postoperative. Le balancias metabolic de aqua, natrium, e chlorido esseva observate in 27 patientes. In le periodo immediatemente postoperative le nivello del natrium seral se abassava a infra 131 mEq per litro in 16 casos; le chlorido seral cadeva a infra 99 mEq per litro in omne casos excepte un, e a infra 90 mEq per litro in 11 casos. Le valores levemente negative in le balancias de natrium e chlorido non sufficeva, per se, a explicar in ulle caso le grado del hyponatremia observate. Notabile transferimentos intracellular de natrium (plus que 100 mEq, con le valores pro

chlorido usate como referentia) se associava con hyponatremia in solo tres casos. Le retention de aqua in le periodo immediatemente postoperative (corrigite in consideration del perditas insensibile) sufficeva pro explicar le observate hyponatremia in omne casos excepte tres, ben que le ration de fluidos prendite non esseva ben correlationate con le occurrentia de hyponatremia. Iste resultatos indica in iste patientes le presentia de un stimulo antidiuretic inusualmente prolongate e de un etiologia ancora incerte. Con le exception de pauc casos il non es necessari corriger le hyponatremia con sal hypertonic, proque le phenomeno es generalmente transiente, limitate, e essentialmente asymptomatic.

Acknowledgment

The laboratory assistance of Mrs. Ruth Miller and Miss Jacqueline McClave is especially acknowledged for the studies reported herein.

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Norepinephrine and Epinephrine Content of Normal and Diseased Human Hearts

By WILHELM RAAB, M.D. AND WILDA GIGEE, A.B.

Because of the exquisitely oxygen-wasting and potentially hypoxia-producing effect of epinephrine on the myocardium, its relative (compared with norepinephrine) and absolute concentration in 85 human hearts was investigated. Significant increases above normal were found in cases of fresh myocardial infarction, in congestive heart failure, and in renal uremia. It is believed that the hypoxiating action of excess epinephrine in the heart muscle constitutes an important pathogenic factor in the origin of certain forms of functional and degenerative heart disease. Prolonged illnesses of various kinds seem to reduce the myocardial norepinephrine content.

THE pathogenic significance of sympathetic stimuli and of hormonal discharges from the adrenal medulla in the origin of functional and degenerative types of heart disease is generally interpreted only in terms of their influence upon cardiac muscular work. Hardly any attention is being paid in clinical thinking to the fact that the adrenosympathogenic catecholamines (epinephrine and probably also norepinephrine) cause a wastage of oxygen by the heart muscle which by far exceeds the simultaneous oxidative energy requirements for mechanical work.[8, 11, 13, 15, 16] Unless compensated by coronary dilatation or by cholinergic oxygen-preserving counterregulation, these oxygen losses are capable of leading to severe, ultimately painful and even necrotizing myocardial hypoxia.[16, 36] The constant presence of relatively large quantities of catecholamines in the heart muscle[19, 25, 37] can be expected to constitute under certain circumstances a serious threat to metabolic and structural myocardial integrity.

Studies on whole animals revealed a considerably greater oxygen-consuming effect of epinephrine compared with that produced by injected norepinephrine.[27, 29] According to Lundholm,[29] it is about 10 times that of norepinephrine, and on the denervated mammalian heart it was found by Gollwitzer-Meier and Witzler[17] to be approximately four times greater than that of norepinephrine. v. Euler[10] even doubts that norepinephrine acts upon the heart as an "oxygen waster" at all. However, the experiments of Eckstein and coworkers[8] seem to disprove this view in that they revealed a marked oxygen wastage by the myocardium during electrical stimulation of the cardiac sympathetic nerves which, in our own experience,[39] elicits in the heart muscle an augmentation of norepinephrine but not of epinephrine.

In view of the greater, potentially more hypoxiating, calorigenic properties of epinephrine, as compared with norepinephrine, it seemed of interest to investigate not only the total catechol concentration in normal and pathological human hearts, as one of us (W. R.) had done before,[32] but also the quantitative mutual relationship of norepinephrine and epinephrine. Normally, norepinephrine constitutes the bulk of the cardiac catechols in all mammalian species so far examined.[25, 37, 39] Only in three out of seven human hearts studied by Holtz and co-workers[25] did the amount of epinephrine exceed that of norepinephrine.

METHODS

Pieces of left ventricular muscle, each weighing at least 40 Gm. were excised from 85 human hearts near the left coronary artery. They were worked up both colorimetrically for total catechols, and by bioassay for the separate evaluation of epinephrine and norepinephrine. In cases of myocardial in-

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This study was aided, in part, by a grant (H-698) from the U. S. Public Health Service, National Heart Institute.

farction, care was taken to use only those areas of the myocardium which were not directly involved.

Only specimens, obtained less than 12 hours after death, were used. Intact myocardial tissue which was left standing at room temperature up to 24 hours showed a loss of color and of pharmacodynamic activity amounting to 11 to 20 per cent. No significant alteration of the mutual proportion of pharmacodynamically active epinephrine and norepinephrine occurred during this period of time. Extracts, made from the heart muscle, could be kept several days in the refrigerator without any major change of chromogenicity and pharmacodynamic activity.

For bioassay, the hearts were extracted and study by the method of v. Euler,[9] as described by Goodall,[19] Holtz[25] and Hökfelt,[23] using as test objects the blood pressure of atropinized, hourly cocainized cats with the adrenals tied off, and the isolated rectal cecum of hens (fig. 1). In the Tyrode solution used for suspension of the latter, a potassium chloride concentration of 0.015 per cent proved most suitable to maintain a constant reactivity. If two or more extracts were assayed on the same cecum, the sensitivity of the preparation was checked between the individual test runs and responses to following extracts were related to these preceding controls.

For calculation of the results, the symbols A, a, Q and q were used in conformity with the usage of other authors.[19, 23, 25] The figures corresponding to these symbols were, as a rule, averages of five or more individual readings obtained with doses of norepinephrine and epinephrine and with extract volumes, respectively, which amounted to at least 10-fold maximum of the initial dosage or extract volume (fig. 1). We found this necessary to avoid errors caused by the fact that the increase of the individual dose responses is not a linear one. Curve amplitudes which did not exactly coincide with those produced by standard doses of norepinephrine were interpolated between the latter, and the norepi-

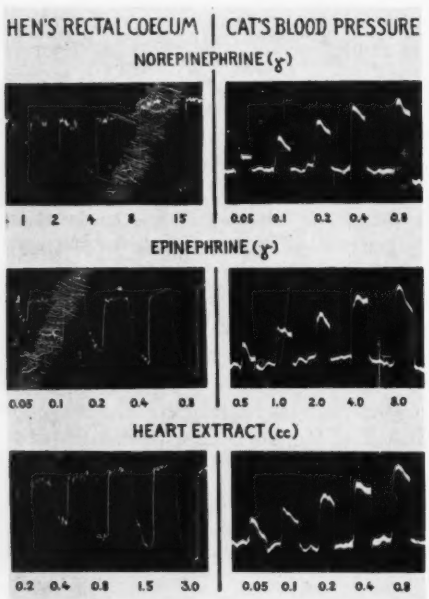

FIG. 1. The effects of mounting doses of norepinephrine, epinephrine and heart extract, respectively, on the isolated rectal cecum of the hen (left) and on the blood pressure of the atropinized, cocainized cat (right). The "norepinephrine equivalents" for 1 gamma epinephrine and for 1 cc. heart extract are computed by dividing the individual doses of norepinephrine used, by those doses of epinephrine and heart extract, respectively, which produce reactions of the same magnitude on the same test object, and by taking the average of each group of reactions. For instance, in the above schematic example, the "norepinephrine equivalents" of the epinephrine doses used on the cecum are 20, 20, 20, 20, 18.75 (average: 20). Thus, 20 microgram norepinephrine are equivalent of 1 gamma epinephrine on the cecum. The "norepinephrine equivalents" for 1 gamma epinephrine on the blood pressure of the cat, and for 1 cc. heart extract on cecum and blood pressure, respectively, are obtained in the same manner. By using symbols, as indicated below, the amounts of epinephrine and of norepinephrine in gamma per cc. heart extract (b, d), and the percentile portions of epinephrine and norepinephrine (e, f) can be calculated as follows:

Q = norepinephrine equivalent of 1 microgram epinephrine on coecum

A = norepinephrine equivalent of 1 cc. heart extract on coecum

q = norepinephrine equivalent of 1 microgram epinephrine on blood pressure

a = norepinephrine equivalent of 1 cc. heart extract on blood pressure

b = (A − a):(Q − q) = microgram epinephrine per cc. heart extract

d = A − (Q × b) = microgram norepinephrine per cc. heart extract

e = 100 b:(b + d) = % epinephrine (related to sum of epi. + norepi.)

f = 100 − e = % norepinephrine (related to sum of epi. + norepi.)

g = b:(gram tissue per cc extract) = microgram epinephrine per gram heart muscle

h = d:(gram tissue per cc extract) = microgram norepinephrine per gram heart muscle.

Example: Q = 20; A = 5; q = 0.1; a = 1; b = 0.2; d = 1; e = 17%; f = 83%; gram tissue per cc. extract = 10; g = 0.02 microgram/Gm.; h = 0.1 microgram:Gm.

nephrine equivalents were then estimated. The absolute quantities (in micrograms) of epinephrine and norepinephrine recovered per cubic centimeter of extract were designated as b and d respectively, and the absolute amounts of epinephrine and norepinephrine per gram of tissue were calculated by dividing b and d by the number of grams of tissue, which corresponded to each cubic centimeter of extract (usually 10). The epinephrine portion (expressed in per cent of the sum of epinephrine and norepinephrine recovered) was designated as e, and the norepinephrine portion (100 − e) as f.

While control tests indicated a sufficient accuracy of the determined epinephrine-norepinephrine ratio in the heart extracts, we do not feel certain of the reliability of the absolute values obtained for these substances. Pure model solutions of synthetic epinephrine and norepinephrine were subjected to the same absorption and elution processes as the heart extracts. The final solutions did not show a loss of catechol chromogenicity, but losses of pharmacodynamic activity were great and irregular, ranging from 40 to 92 per cent. This would seem to disqualify the method in question for quantitative assay purposes if it were not known that chemically pure epinephrine is much more labile and more easily inactivated than epinephrine from biological sources, which is believed to be "protected" by accompanying lipids and proteins. The latter concept seems to be supported by our observation that the losses of activity of large doses of epinephrine and norepinephrine which were injected in dogs and subsequently recovered from their hearts, were considerably smaller than those of synthetic model solutions. Indeed, in some instances the entire portions of injected epinephrine and norepinephrine which had been absorbed by the heart muscle (as estimated by colorimetry) were recovered by bioassay. Known amounts of epinephrine and norepinephrine added to the heart extracts showed likewise relatively small losses (about 24 per cent).[23] Thus, it may be assumed that the catechol recoveries from the heart muscle by bioassay represent most of the original active material but their absolute accuracy and regularity remains somewhat questionable. The usually large discrepancy between colorimetrically and pharmacodynamically demonstrable total cardiac catechols is probably ascribable, in part, to the presence of chromogenic but pharmacodynamically more or less inactive catechols in the myocardium, a view which is shared by Goodall.[19]

The colorimetric determinations of total cardiac catechols were carried out with the modified method of Shaw,[44] as described by one of us (W. R.) elsewhere,[32] except that the epinephrine standard readings were kept constant by means of a Coleman photoelectric colorimeter. For unknown reasons, possibly inherent in differences in the reagents used, the colorimetric values of the present series were appreciably higher than those of the findings reported in earlier publications.[32, 33, 34] The colorimetric results are expressed in color units per gram of fresh tissue, each unit equalling the color intensity of 0.001 microgram of epinephrine. They include certain other catecholamines, related to but not identical with norepinephrine and epinephrine (e.g. dihydroxyphenylalanine and hydroxytyramine).

Results

Table 1 shows the values obtained in a total of 85 hearts. Fifty-one of these were the hearts of persons who had not displayed any subjective or objective signs of cardiac anomaly before death. (Ten patients with hypertension but without clinical cardiac manifestations are included in this group). Thirty-four were the hearts of patients who had suffered from chronic or acute congestive heart failure, fresh myocardial infarction (less than 10 days before death), arterial hypertension (blood pressure levels of 150/90 or more), and renal uremia accompanied by congestive failure. Some showed post mortem cardiac hypertrophy (450 Gm. or more), coronary sclerosis of a significant degree, and microscopically discernible degenerative myocardial lesions. Obviously, there was considerable overlapping of these different categories, as represented in table 1 and figures 2, 3 and 4.

Epinephrine-Norepinephrine Relations (*Bioassay*). Epinephrine constituted on an average 13 per cent of the total active catecholamines recovered from the hearts of the 51 noncardiac persons (fig. 2). Setting the limit of normal at 30 per cent, there were only 5 out of the 51 cases (10 per cent) in which the epinephrine was at or above this limit (fig. 3). In nine cases (18 per cent) there was no epinephrine demonstrable at all.

In all groups of clinically diseased hearts, the average epinephrine percentages were higher than in the noncardiac group (fig. 2). The highest average (50 per cent) of epinephrine was found in the cases of fresh myocardial infarction. Only one out of the seven cases of this group had an epinephrine percentage below 30 per cent.

The next highest average epinephrine percentage was found in the cases of congestive heart failure. None was epinephrine-free. After this follow the overlapping groups of

TABLE 1.—*Total Catechols (Colorimetry) and Pharmacodynamically active Catechols (Epinephrine; Epinephrine plus Norepinephrine; Bioassay) in Human Left Ventricular Muscle*

Category of Cases	No. of Cases	Total Catechols* (cu/Gm)		Epinephrine (% of Active Catechols)†		% Cases with 30 or More % Epinephrine	No. of Cases‡	Recovered Active Epinephrine§ (γ/Gm.)		Recovered Total Active Catechols‖ (γ/Gm.)	
		Average	Standard deviation	Average	Standard deviation			Average	Standard deviation	Average	Standard deviation
Clinically noncardiacs	51	1531	±110	13	±1.7	10	38	0.012	±0.003	0.143	±0.030
Fresh myocardial infarction	7	1510**	±440	50#	±10.0	86	5	0.038**	±0.018	0.081	±0.021
Congestive heart failure	28	1788**	±160	36#	±3.8	54	20	0.020**	±0.006	0.056	±0.009
Renal uremia	14	1922**	±270	25#	±4.0	28	11	0.016**	±0.007	0.055	±0.014
Essential hypertension	30	1683	±760	24	±17.0	30	23	0.011	±0.009	0.052	±0.010
Cardiac hypertrophy	24	1819	±835	23	±14.1	38	19	0.011	±0.010	0.051	±0.031
Myocardial degeneration	42	1584	±790	28	±20.4	36	31	0.016	±0.021	0.071	±0.082
Coronary sclerosis	45	1549	±711	25	±20.8	36	34	0.014	±0.018	0.072	±0.047

* Determined by colorimetry (Shaw's method). Color units per gram of tissue.

† Epinephrine, expressed in per cent of the sums of recovered epinephrine plus norepinephrine, as determined by bioassay (v. Euler's method).

‡ The numbers of cases in the following columns are smaller than those in the preceding ones because, in some early tests, only the relative amounts of epinephrine and norepinephrine in relation to each other had been determined.

§ Absolute amounts of epinephrine per gram of tissue, recovered by bioassay.

‖ Absolute amounts of epinephrine plus norepinephrine per gram of tissue, recovered by bioassay.

These figures differ significantly at the 1% probability level (*t* test, Fisher) from the corresponding mean figures of the noncardiac control group.

** The significance of the difference of these figures from the corresponding mean figures of the noncardiac control group is uncertain.

myocardial degeneration, renal uremia (all cases with uremia complicated by congestive failure had more than 30 per cent epinephrine), coronary sclerosis, arterial hypertension and cardiac hypertrophy.

The highest individual epinephrine percentages were found, with one exception, in the hearts of patients who had died in more or less acute congestive failure and with pulmonary edema. They were distributed as follows:

91 per cent: J. B., a 63 year old male who had arteriosclerotic heart disease with recent myocardial infarction and terminal congestive failure. (This case had been referred to in a preliminary publication[37] as having had 100 per cent epinephrine, but this had to be corrected on recalculation);

69 per cent: J. K., a 74 year old male with arteriosclerotic heart disease and old myocardial infarctions who developed terminal congestive failure with pulmonary edema;

66 per cent: M. H. S., a 65 year old male with Kimmelstiel-Wilson syndrome, recent myocardial infarctions and acute congestive failure;

65 per cent: M. E. McK., an 80 year old female with arteriosclerotic heart disease and acute congestive failure;

58 per cent: J. L., a 77 year old male with carcinoma of the stomach, arteriosclerotic heart disease, uremia and congestive failure;

49 per cent: R. G. S., a 55 year old male with coronary disease, who died suddenly with pulmonary edema;

49 per cent: V. D., a 84 year old female with auricular flutter, followed by ventricular fibrillation;

43 per cent: M. N., a 29 year old female

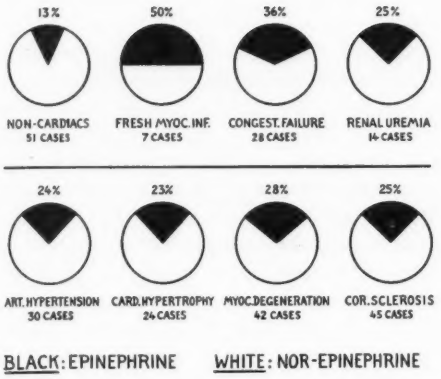

FIG. 2. Mutual relation of epinephrine and norepinephrine (average values).

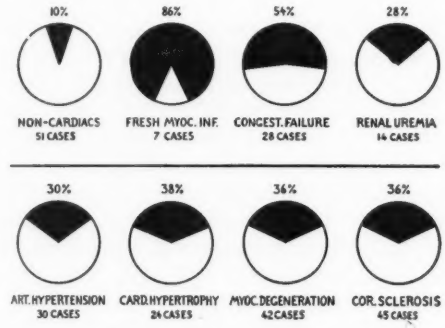

FIG. 3. Percentile occurrence of abnormally high relative epinephrine concentrations in different groups of cardiac pathology.

with pyelonephritis, uremia, terminal congestive failure and pulmonary edema;

40 per cent: C. J., a 85 year old male with probable thiamine deficiency, myocardial infarction, terminal congestive failure and pulmonary edema;

52 per cent: E. H., a 56 year old female with ovarian cystadenoma and metastases; but no history or postmortem findings suggestive of heart disease.

Absolute Amounts of Epinephrine (Bioassay) (fig. 4). An average of 0.012 microgram of epinephrine per gram of heart muscle was found in the group of clinically undiseased hearts. The highest average amount (0.038 microgram per gram) of epinephrine was observed in the hearts of patients with fresh myocardial infarction, followed in that order by the groups of patients with congestive failure, renal uremia, myocardial degeneration, and coronary sclerosis. The average epinephrine values for patients with hypertrophied hearts and for those with hypertension were about equal to those of the noncardiac subjects.

The total recovered active catecholamines (averages of epinephrine plus norepinephrine) appeared to be highest in the noncardiac group (fig. 4), followed in that order by the groups with fresh myocardial infarction, coronary sclerosis, myocardial degeneration, congestive failure, uremia, hypertension, and cardiac hypertrophy.

The combined norepinephrine plus epinephrine readings occupied a wide range (minimum

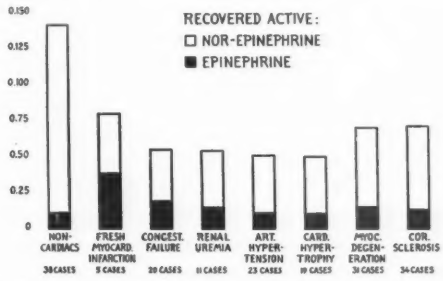

FIG. 4. Absolute bioassay values of recovered epinephrine and norepinephrine (averages).

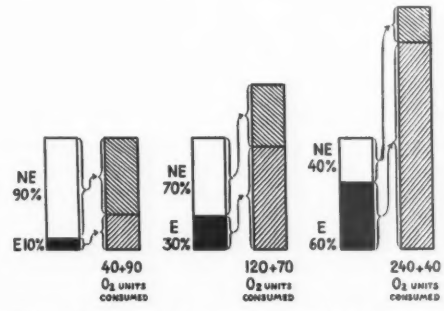

FIG. 5. Presumable oxygen-consuming effect of increasing percentages of epinephrine within a constant total quantity of active catechols, based on the finding of Gollwitzer-Meier and Witzler[17] that epinephrine consumes approximately four times as much cardiac oxygen as norepinephrine.

0.009 microgram per gram, maximum 1.017 microgram per gram). It seems worthy of note that all of five readings which were exceptionally high, due to unusually large amounts of norepinephrine, were observed in cases of sudden, unexpected death;

1.017 microgram per gram: L. N. Q., a 33 year old male who was shot through the heart with a shotgun and died instantly;

0.460 microgram per gram: R. P., a 29 year old male with compensated mitral stenosis who died suddenly and unexpectedly with pulmonary edema;

0.425 microgram per gram: J. E. E., a 35 year old male, who died suddenly and unexpectedly from acute coronary occlusion, caused by an atherosclerotic plaque, but had no myocardial infarction;

0.404 microgram per gram: H. H. B., a 48 year old male who was buried under falling logs and died within 90 minutes;

0.400 microgram per gram: J. W. F., a 19 year old male student who died suddenly while attending class at college and showed at necropsy multiple necroses and thromboses of arterioles in the brain stem.

Total Catechols (Colorimetry). The average of colorimetric total catechol readings was lowest in the noncardiac group and highest in the uremia group, with the cardiac hypertrophy and congestive failure groups next, and the other groups near the normal average.

Relation Between Total Catechols and Norepinephrine Plus Epinephrine. This ratio (microgram per gram norepinephrine plus microgram per gram epinephrine: total catechols, expressed as color "macrounits"* per gram) varied between a minimum of 0.003 and a maximum of 0.590 with an average of 0.082. The highest ratios (0.572, 0.590, 0.390, 0.331, and 0.260 respectively) were found in the same five cases of sudden death who had the highest combined norepinephrine plus epinephrine values.

* One "macrounit" corresponds to 1000 ordinary color units and is equal in color intensity to one microgram of epinephrine.

Discussion

Most of our absolute bioassay values fo active epinephrine and norepinephrine in th human heart were lower than those obtaine by Holtz and co-workers[25] in seven huma hearts, the only ones so far published, but th average epinephrine percentage was nearly th same (26 per cent compared with 27 per cent) It is not apparent from the data of the Germa workers whether their series included an pathological hearts.

The following salient points evolve fro our own observations:

(1) *The mutual quantitative proportion o epinephrine and norepinephrine in clinicall nondiseased human hearts was similar to tha observed in other mammalian species* (cattle, pig, rabbit, sheep, guinea pig, rat),[25, 37] namely, a definite preponderance of norepinephrin over epinephrine.

(2) *In all categories of pathological human hearts, there was a greater incidence of abnormally high epinephrine percentages in relation to norepinephrine than in nonpathological specimens.* This anomaly was statistically definitely significant in the groups with fresh myocardial infarction and with congestive heart failure, including the group with uremia. The highest relative epinephrine concentrations were found in the hearts of patients with acute congestive heart failure and pulmonary edema. An abnormal increase of epinephrine in failing human hearts had also been suspected by one of us (W. R.) in 1943 from colorimetric observations.[32]

(3) *The absolute amounts of active epinephrine, recovered by bioassay, were greatest in patients with fresh myocardial infarction, followed by those with congestive heart failure and uremia.* On the other hand, the average total amounts of recovered active epinephrine and norepinephrine combined were lower in all pathological groups than the group of clinically normal hearts. This feature suggests that the excess amounts of epinephrine found in pathological hearts might have been formed locally at the expense of norepinephrine by methylation of the latter rather than by discharge fro

the cardiac chromaffin cell islands,[45, 46] or by transportation from the adrenal medulla via the blood stream. Norepinephrine is believed to be the natural nonmethylated precursor of epinephrine.[2, 24] Thus, one may suspect the existence of enzymatic derangements in the heart muscle which are capable of upsetting the normal epinephrine-norepinephrine ratio. The greater susceptibility of norepinephrine to destruction by aminoxidase, compared with that of epinephrine[3], may also somehow contribute to the relative prevalence of the latter in pathological hearts.

The assumed local methylation process seems to be especially active in freshly infarcted and in failing hearts. Recent observations by Harris and co-workers[21] on artificially infarcted dog hearts were similarly interpreted by these authors as suggesting a local activity of sympathomimetic catechols.

(4) *In the cases of renal uremia, the higher colorimetric values for total catechols, as well as the increased amounts of epinephrine* are probably caused by the absorption of catechols from the blood. These substances accumulate in uremic blood in excessive quantities,[35] apparently due to renal retention,[38] and the tendency of the heart muscle to "trap" and store circulating catechols is a well-established phenomenon.[32, 37] An even more striking augmentation of the total chromogenic myocardial catechols in uremic human hearts had been observed in 1944 (35) by one of us (W. R.). Hökfelt[23] reported an increase of the myocardial catecholamines in nephrectomized cats.

(5) The comparatively frequent occurrence of high relative and/or absolute epinephrine concentrations in the hearts of persons with arterial hypertension, cardiac hypertrophy, coronary sclerosis and structural myocardial degeneration coincided in most of the cases with congestive failure or myocardial infarction.

(6) The strikingly high absolute norepinephrine concentrations and the correspondingly high ratios of pharmacodynamically active to inactive chromogenic catechols in the hearts of persons who had died suddenly and unexpectedly from acute vascular or traumatic accidents seemed to represent an analogy to the comparatively high absolute norepinephrine content of the hearts of various species of suddenly killed, healthy experimental animals.[37] They suggest that in more or less undisturbed general health, the norepinephrine deposits in the heart are to a lesser extent subjected to enzymatic destruction, or else are more readily replenished by sympathetic neurosecretion, than in prolonged illnesses of various kinds. No abnormally high colorimetric readings for total catechols were obtained in the five cases under question in contrast to two cases published elsewhere[33, 34] who died suddenly without any obvious organic pathology and in whom an excessive accumulation of catecholamines, especially of epinephrine, in the heart muscle had been suspected as the cause of sudden cardiac death. No differentiation of norepinephrine and epinephrine by bioassay was carried out in those cases.

The inclusion of cases of sudden death with exceptionally high cardiac norepinephrine concentrations in the noncardiac group is in part responsible for the high norepinephrine average (fig. 4) of this group.

Conclusions

The approximately 4- to 10-times greater oxygen consumption-promoting effect of epinephrine, compared with that of norepinephrine,[17, 29] makes it appear likely that the abnormally large amounts of epinephrine which were found in many pathological hearts constitute an important pathogenic factor, since epinephrine is an exquisitely oxygen-wasting, efficiency-impairing and ultimately anoxiating agent. This applies especially to congestive heart failure, to the early state of the heart after myocardial infarction, and to the cardiac complications of renal uremia. Figure 5 shows that a relatively small augmentation of epinephrine within a given total amount of active catechols will produce a disproportionately marked increase of wasteful and potentially hypoxiating oxygen consumption.

Abnormally augmented epinephrine per-

centages were also found with an increased but less significant frequency in hearts from hypertensive persons and in hypertrophic, microscopically degenerated and coronary sclerotic hearts. These groups overlap largely with the epinephrine-rich groups of congestive failure and myocardial infarction, and it is not possible at this time to ascribe a primary specificity of the cardiac epinephrine augmentation to such chronic conditions as essential hypertension, coronary sclerosis and lingering myocardial degeneration. In most instances, these conditions must have existed over long periods before death occurred, and one may only speculate by inference that catechol activity in the heart muscle might have contributed to their development.

The presumable pathogenic role of norepinephrine as an oxygen waster of lesser cardiac toxicity than epinephrine is still under debate. However, it may be well to refute at this point the widespread erroneous conception that the bradycardia-producing effect of artificially administered norepinephrine and its beneficial action in cardiogenic shock prove its inherent harmlessness. The favorable reactions, produced by injected, circulating (but not by intramyocardially discharged sympathogenic) norepinephrine are due to the provocation of secondary overwhelming counterregulatory vagal effects on the heart, caused by stimulation of the peripheral pressoreceptors and possibly by the Bezold-Jarisch reflex mechanism. This can be readily demonstrated by elimination of the secondary vagal effects through atropine or vagotomy which makes all the specific, epinephrine-like cardiac effects of norepinephrine, per se, appear unhampered[14, 17 and 43]. Artificially injected norepinephrine is an ideal indirect stimulant of the myocardial oxygen-preserving vagus, but norepinephrine, physiologically liberated at the sympathetic nerve endings in the heart muscle, acts upon the latter as a purely sympathomimetic epinephrine-like agent,[17, 28] even though endowed with much weaker oxygen-wasting properties than epinephrine.[17]

The assumption that interference of sympathomimetic catechols, and particularly of epinephrine, in myocardial metabolism precipitates congestive heart failure, is made probable by various clinical and experimental facts:

(a) the experimental production of acute left ventricular failure and pulmonary edema by injection of epinephrine which is eagerly absorbed and accumulated by the heart muscle;[32, 37]

(b) the promotion of congestive heart failure by thiamine deficiency which is accompanied by an accumulation of excess catecholamines in the heart muscle;[19, 41] indications of thiamine deficiency in chronic congestive heart failure;[47]

(c) the aggravation of existing congestive heart failure by exercise which is accompanied by an accumulation of excess catecholamines in the heart muscle;[23, 32]

(d) the analogy of the wasteful, inefficient oxygen consumption, induced by epinephrine, and that found in the failing human heart;[1, 18]

(e) the analogies of epinephrine-induced alterations of myocardial intermediate metabolism[7, 31, 42] with those found in decompensated human hearts, such as depletion of creatine and phosphorus;[6, 22, 30]

(f) the favorable therapeutic results of sympathectomy which reduces the myocardial catecholamines,[19, 40] as observed in some cases of severe congestive failure;[5, 12, 26]

(g) the therapeutic action of the digitalis glycosides which improve myocardial oxygen economy and oxidative efficiency[1, 20] in direct opposition to the oxygen-wasting, inefficiency-producing effect of the catechols.

Our present observations seem to add another piece of indirect evidence to the above enumerated arguments in favor of a fundamental pathogenic role of the sympathomimetic catecholamines, notably epinephrine, in the myocardial metabolic origin of congestive heart failure and of the functional cardiac complications following myocardial infarction.

Summary

Colorimetric determination of total catecholamines, and bioassay of norepinephrine and epinephrine separately were carried out in

85 human hearts. Certain shortcomings of the available methods are discussed.

The findings confirmed the observation, made by other workers in other mammalian species, that the bulk of the pharmacodynamically active catechols in the heart consists of norepinephrine while epinephrine constitutes only a relatively small fraction.

A significant relative and absolute increase of epinephrine was found in the heart muscle of persons who had died after a fresh myocardial infarction, of those in congestive heart failure, and of patients with renal uremia. The highest relative epinephrine concentrations were observed in cases with acute congestive failure and pulmonary edema.

The comparatively frequent finding of augmented myocardial epinephrine in cases of such chronic conditions as essential hypertension, cardiac hypertrophy, myocardial degeneration and coronary sclerosis coincided, as a rule, with the presence of congestive failure of myocardial infarction.

In view of the highly oxygen-wasting, efficiency-impairing and potentially hypoxiating properties of epinephrine, it is assumed that its abnormal augmentation in the heart muscle constitutes an important pathogenic factor in congestive heart failure and in other forms of functional and degenerative heart disease, especially if vagal counterregulation and/or coronary blood supply are inadequate.

The possible origin of the excess amounts of epinephrine found in diseased hearts is discussed. In uremia, excess quantities seem to accumulate as a sequel to renal catechol retention.

The high norepinephrine concentrations present in the hearts of more or less healthy persons, who had died suddenly and unexpectedly from vascular or traumatic accidents, are believed to represent a normal rather than a pathological feature, in contrast to a norepinephrine depletion of the heart in various types of prolonged, fatal illnesses.

Summario in Interlingua

Esseva executate determinationes colorimetric del catecholaminos total e bioessayos separate del norepinephrina e epinephrina in 85 cordes human. Es discutite certe disavantages del methodos nunc disponibile.

Nostre constatationes confirmava le observation, facite per altere recercatores qui ha laborate con altere species mammifere, que le grosso del pharmacodynamicamente active catecholes in le corde consiste de norepinephrina durante que epinephrina constitue solo un fraction relativemente parve.

Un significative augmento relative e absolute de epinephrina esseva trovate in le myocardio (1) de personas qui habeva morite post nove infarcimentos myocardiac, (2) de personas in dysfunctionamento cardiac congestive, e (3) de patientes con uremia renal. Le plus alte concentrationes relative de epinephrina esseva observate in casos con acute dysfunctionamento congestive e in casos con edema pulmonar.

Le constatation comparativemente frequente de augmentate epinephrina myocardiac in casos de tal chronic conditiones como hypertension essential, hypertrophia cardiac, degeneration myocardiac, a sclerosis coronari coincidava generalmente con le presentia de dysfunctionamento congestive o de infarcimento myocardiac.

In vista del facto que epinephrina es un grande guastator de oxygeno e degradator de efficacia e que illo es potentialmente hypoxiante, nos assume que su augmentation anormal in le myocardio constitue un importante factor pathogene in congestive dysfunctionamento cardiac e in altere formas de morbos cardiac functional e degenerative, specialmente si le contraregulation vagal e/o le apporto de sanguine coronari es inadequate.

Es discutite le possibile origine del excesso de epinephrina in cordes morbose. In uremia le accumulation excessive pare esser un sequela del retention de catechol renal.

Le alte concentrationes de norepinephrina in le cordes de plus o minus valide personas qui moriva subitemente e inexpectatemente in consequentia de accidentes vascular o traumatic representa, secundo nostre opinion, un tracto normal plus tosto que pathologic, in contrasto al relative depletion de norepinephrina in le corde de patientes con varie typos de morbos prolongate e fatal.

Acknowledgments

We are indebted for the specimens to the Departments of Pathology of the Bishop DeGoesbriand Hospital (Dr. E. Stark) and of the Mary Fletcher Hospital (Dr. E. Woll), and to Dr. J. W. Spelman, State Pathologist. Dr. W. v. B. Robertson of our Division kindly carried out the calculations of the Fisher *t*-test.

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The Use of Hexamethonium in Treatment of Arteriosclerosis Obliterans

By JOHN H. WINDESHEIM, M.D., GRACE M. ROTH, PH.D. AND RAY W. GIFFORD, JR., M.D.

The effect of hexamethonium on hypertension has been widely studied but its effect on the peripheral blood vessels of patients with severe occlusive vascular disease has been studied on only a few patients although the drug has been used empirically in the treatment of such disease.

Observations were made on the effect of hexamethonium ion administered subcutaneously in increasing doses of 10 to 50 mg. on the skin temperature of the fingers and toes, the blood pressure and the pulse rates of a group of patients with severe arteriosclerosis obliterans. On this group of patients hexamethonium had little or no effect.

SINCE hexamethonium was introduced by Paton and Zaimis,[1] its use in the treatment of hypertension has been widely studied, but few authors have reported on its effect on peripheral vascular disease.

The hexamethonium ion causes peripheral vasodilatation by blocking the transmission of nerve impulses across sympathetic ganglia. Schnaper and associates[2] noted that the increase in blood flow in the foot after intravenous administration of 50 to 100 mg. of the hexamethonium ion in 10 normal subjects was not significantly different from that obtained after intrathecal or epidural lumbar anesthesia. This suggested that the degree of blockade of sympathetic vasoconstrictor impulses to the feet was nearly complete after intravenous injection of 50 to 100 mg. of hexamethonium ion. Burt and Graham[3] studied the effect of hexamethonium on five normal subjects, 15 patients with arteriospastic disease, but without occlusive arterial disease and seven patients with hypertension. They noted greater vasodilatation in the lower than in the upper limbs following intravenous injection of 30 to 40 mg. of pentamethonium and hexamethonium ions. The skin temperature of the toes of the normal subjects rose 8.5 C. while that of the patients with vasospastic disease rose 7.9 C. after injection of these drugs. Finnerty and Freis[4] observed the effect of intravenous injection of 20 to 100 mg. of hexamethonium ion on 22 subjects, "some of whom suffered from various types of peripheral vascular disease." In all cases except those of organic obstruction of the larger arteries the skin temperature and blood flow in the digits, particularly in the toes, were markedly elevated. The same authors[5] later reported good clinical results from use of hexamethonium in the treatment of various peripheral vascular diseases, including arteriosclerosis obliterans in five cases. They claimed from their study that it was as effective as paravertebral block. Kvale[6] in a recent review of the treatment of occlusive arterial disease, stated that subcutaneous injections of hexamethonium may be of value in selected cases in which sympathectomy may not be advisable.

The present study was undertaken to evaluate the usefulness of hexamethonium in the treatment of patients with severe arteriosclerosis obliterans.

METHOD

The observations were made on 14 hospitalized patients who had severe arteriosclerosis obliterans in the lower limbs. There were 12 men and 2 women with an age range of 50 to 78 years, and a mean age of 64 years. Their basal metabolic rates ranged from −28 to +14 per cent.

Data were obtained in a room in which the temperature was 25 to 27 C. and the relative humidity was 40 per cent. The subjects fasted and received no medication of any kind for 15 hours before the test. During the tests they wore lightweight short pajamas and lay supine on comfortable beds. The basal metabolic rate was determined during the control period.

The skin temperature of the fingers and toes was employed as a means of measuring vasoconstriction

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TABLE 1.—*Pulse Rate, Blood Pressure and Skin Temperature of Fingers and Toes Before and After Injections of Hexamethonium Ion*

Patients	Dose in mg.	Pulse Rate, Beats Per Min.			Blood Pressure in mm. of Hg						Skin Temperature in Degrees C.					
					Before		After		Difference		Toes			Fingers		
		Before	After	Difference	S.	D.	S.	D.	S.	D.	Before	After	Difference	Before	After	Difference
14	10	72	80	+8	157	92	118	73	−39	−19	29.1	29.4	+0.3	33.0	33.2	+0.2
6	20	65	72	+7	127	75	109	66	−18	−9	28.8	29.2	+0.4	32.2	33.1	+0.9
9	30	67	75	+8	143	85	114	72	−29	−13	28.6	29.1	+0.5	32.1	33.0	+0.9
6	40	65	73	+8	132	74	99	65	−33	−9	28.2	29.4	+1.2	31.5	32.3	+0.8
11	50	67	79	+12	150	88	106	66	−46	−22	28.6	29.2	+0.6	32.6	33.5	+0.9

and vasodilatation of the extremities. The temperature of the plantar surfaces of the first, third and fifth toes of both feet and the volar sides of the distal phalanges of the third finger of both hands was measured by means of copper constantan thermocouples. After a control period of about an hour, when the cutaneous temperature had become stabilized and determinations of basal blood pressure and pulse rate had been made, hexamethonium ion was administered subcutaneously. Readings of skin temperature, blood pressure and pulse rate were taken every 5 to 10 minutes for at least 90 minutes. Each patient was given 10 mg. of hexamethonium ion subcutaneously the first day, and it was our intention to increase the dose of hexamethonium ion by 10 to 20 mg. on consecutive days until a dose of 50 mg. was reached. Due to the marked hypotensive effect of the drug on several elderly patients, it was felt unwise to subject them to further episodes of marked hypotension. Thus only 11 of the original 14 patients received 50 mg. subcutaneously.

Results

The findings for the total group of patients are shown in table 1 and in figure 1. In this and following graphs (figs. 2 to 5) the average basal skin temperatures of the three toes and of the fingers before treatment are compared with the average of the maximal responses of the three toes and the fingers to the drug. The pulse rate was increased by 8 to 12 beats per minute following the injections of hexamethonium and the systolic and diastolic blood pressures measured in the supine position decreased 18/9 to 46/22 mm. with increasing doses of hexamethonium. As stated previously the fall in the systolic and diastolic blood pressure after 10 mg. was greater than after 20 to 40 mg. because the three patients could not tolerate larger doses of the drug and thus did not receive them. The skin temperature of the fingers and toes showed little change following injection of 10 to 50 mg. of hexamethonium ion subcutaneously. The drop in blood pressure occurred within 15 to 30 minutes after the injection in all patients, and the skin temperature began to increase during this period in the few patients who showed a response to the drug. The peak skin temperature was reached between one and one-half and two hours after the injection.

Of the total of 14 patients, two had a rise in skin temperature of the toes following the larger doses of hexamethonium, two demonstrated an increase in skin temperature in the less affected lower limb only, and 10 did not show any increase in the skin temperature of the toes following the injections of hexamethonium.

An example of each type of reaction will be shown in the following brief case reports.

Case 1. A white man, 68 years old, complained of a nonhealing ulcer which had been present on the

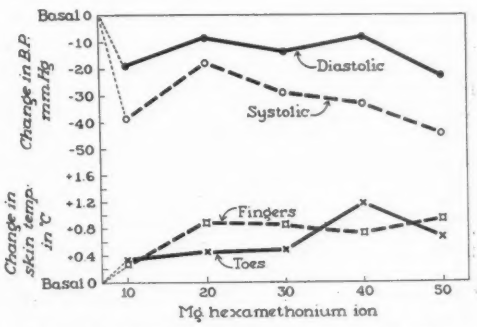

FIG. 1. Change in skin temperature and blood pressure following increasing doses of hexamethonium ion in the total group of patients.

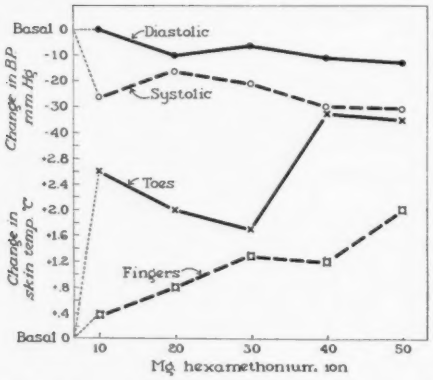

FIG. 2 (case 1). Change in blood pressure and skin temperature in response to increasing doses of hexamethonium ion.

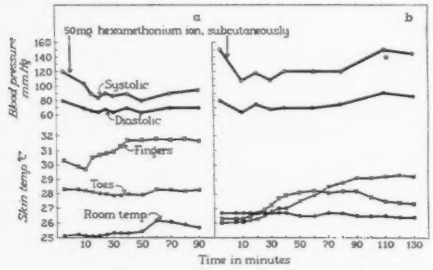

FIG. 3. Response of blood pressure and skin temperature to 50 mg. of hexamethonium ion. *a*. Case 2. *b*. Case 1.

left great toe for two years. He was otherwise asymptomatic. Examination revealed the pulse in the femoral arteries to be normal. The popliteal pulses were diminished, and pulses were absent bilaterally from the dorsalis pedis and posterior tibial arteries. There was mild pallor on elevation of the legs with dependent rubor. The venous filling time was 45 seconds in the right leg and 35 seconds in the left. A small ulcer was present on the medial aspect of the left great toe. The basal metabolic rate ranged from −21 to −28 per cent during the period of testing.

The response to increasing amounts of hexamethonium is shown in figure 2. The skin temperature in the toes rose sharply even with the smallest dose of the drug, while the skin temperature of the fingers changed less, but definitely, with doses of 30 to 50 mg. of hexamethonium ion. Figure 3*b* demonstrates the response to 50 mg. of hexamethonium ion. The skin temperature of the toes increased from 26 to 29.3 C., with the peak occurring two hours after the injection. The skin temperature of the fingers increased also, but the rise was not as marked nor as prolonged as that of the toes. Skin temperature studies made after left lumbar sympathetic block with alcohol demonstrated results almost exactly equal to those following administration of 50 mg. of hexamethonium ion subcutaneously.

Case 2. A white man, 59 years old, had bilateral claudication of the calves for three years. Two months before admission spontaneous gangrene of the right great toe developed which necessitated amputation of the toe. The wound failed to heal and an ulcer 1 cm. in diameter was present at the amputation site on admission. All pulses below the femoral arteries were absent bilaterally and mild pallor of both legs was noted on elevation. Dependent rubor was moderate in the right and the venous filling time was 36 seconds in the right and 12 seconds in the left. The response of the skin temperature to hexamethonium is shown in figures 3*a* and 4. The fingers showed a moderate increase in skin temperature but the skin temperature of the toes did not change even with the larger doses of the drug. The blood pressure usually decreased following injection of hexamethonium.

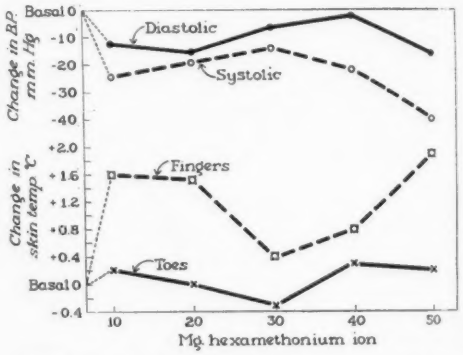

FIG. 4 (case 2). Change in blood pressure and skin temperature in response to increasing doses of hexamethonium ion.

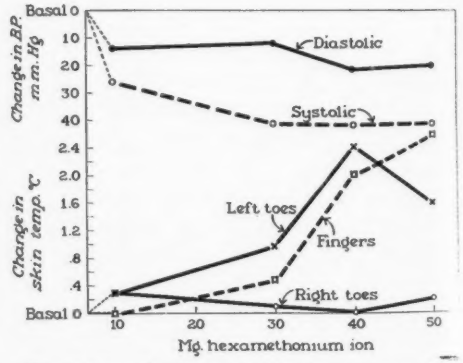

FIG. 5 (case 3). Change in blood pressure and skin temperature in response to increasing doses of hexamethonium ion.

Case 3. A white woman, 71 years old, who had had mild diabetes for 12 years, entered the hospital because of an ulcer which had been present for two months on the lateral aspect of the right foot. She had severe constant pain at the site of the ulcer. Physical examination revealed moderate obesity, a nodular goiter, and an ulcer measuring 2 by 1.3 cm. over the right fifth metatarsal. The pulse in the femoral and popliteal arteries was normal bilaterally, as was the pulse in the dorsalis pedis artery on the left. Pulses were absent from the dorsalis pedis and posterior tibial arteries on the right, and from the posterior tibial on the left. There was moderate dependent rubor on the right, but no pallor on elevation. The response of the skin temperature to hexamethonium is shown in figure 5. It will be noted that the skin temperature of the fingers and of the left foot was increased by the larger doses of hexamethonium, but that of the right foot was unchanged. A right lumbar sympathetic block with alcohol was performed, and studies of skin temperature following it revealed no change from the levels obtained prior to the block.

Four of the 14 patients were studied after lumbar sympathetic blocks with alcohol. The skin temperature of the toes of three of these patients had not responded to hexamethonium, nor was it changed by the block. The fourth patient (case 1) demonstrated vasodilation of the toes after both hexamethonium and the alcohol block (figs. 2 and 3*b*).

Comment

Hexamethonium in the amount given did not cause vasodilatation in the vessels of the lower limbs as measured by skin temperature of the majority of patients with arteriosclerosis obliterans. Since the hypotensive effect of the drug was observed in all patients, vasodilatation must have occurred in some other part of the body. Cranley and associates[7] stated that agents used for vasodilation will have their maximal effect on those areas of the body in which the vessels are most nearly normal and a minimal effect on the area in which organic vascular changes have taken place. Our findings are in agreement with this statement. This was well shown in case 3 in which the less severely involved leg showed vasodilation while the skin temperature of the other leg, in which the greatest effect was desired, did not change.

Possibly larger doses of hexamethonium would have been more effective, although Finnerty and Freis[4] found that intravenous injections of 100 mg. of hexamethonium were no more effective in causing vasodilation than 50 mg. We considered that larger doses would be dangerous for patients of the age of our group because of the hypotensive effect.

Patients with early organic vascular disease, in whom collateral vessels are still able to dilate may respond better than the group of patients with severe occlusive arterial disease. It is the latter group, however, which needs treatment, and failure to cause vasodilation with hexamethonium is the rule in this group.

Summary

Hexamethonium ion in increasing doses of 10 to 50 mg. was given subcutaneously to a group of 11 patients with severe arteriosclerosis of the lower extremities. Three additional patients were given 10 mg. but not the larger doses because of the hypotensive effects of the drug. Two patients responded to the drug with a slight to moderate increase in skin temperature of the toes. Two others showed slight vasodilatation in the less ischemic lower extremity, but none in the limb with more severe arteriosclerosis obliterans. The skin temperature of the toes in the remaining 10 patients did not change after the injections of hexamethonium.

From this study it is concluded that hexamethonium is not effective in the treatment of severe arteriosclerosis obliterans. Since the blood pressure decreased after injection of the drug, we assume that vasodilation occurred in blood vessels unaffected by the arteriosclerotic process.

Summario in Interlingua

Ion de hexamethonium esseva administrate subcutaneemente, in doses progressivemente augmentate ab 10 mg usque a 50 mg, a un gruppo de 11 patientes con sever arteriosclerosis del extremitates inferior. Tres altere patientes, originalmente destinate a sequer le mesme curso, recipeva solmente le administrationes de 10 mg. In iste casos le effectos hypotensive del droga esseva si marcate que le dosages augmentate non pareva consiliabile.

Duo patientes reageva per un leve o moderate augmento del temperatura cutanee del digitos del pede. Duo alteres habeva un leve vasodilatation in illo inter lor extremitates inferior que esseva minus ischemic sed non in illo que esseva plus severmente affligite per arteriosclerosis obliterante. In le remanente 10 patientes le temperatura cutanee del digitos del pede non cambiava post le injectiones de hexamethonium.

Ab iste studio nos conclude que hexamethonium non es efficace in le tractamento de sever arteriosclerosis obliterante. Proque le pression sanguinee decresceva post injectiones del droga, nos suppone que vasodilatation occurreva in vasos sanguinee non afficite per le processo arteriosclerotic.

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Differential Analysis of Opacification in Angiocardiography

A Graphic Interpretation of Cardiac Function

By J. LIND, M.D., R. SPENCER, M.D. AND C. WEGELIUS, M.D.

Each individual exposure in an angiocardiogram gives a picture of the arrested motion of the heart in successive stages of opacification. By combining these isolated views in a graph, a continuous dynamic process can be visualized. The chambers of the heart can be analyzed separately, and by correlating the opacification in the various chambers, the function of the heart as a whole can be studied.

AN interpretation of cardiac function as a whole demands study not only of the active cardiac contractions but also of their secondary effects upon the circulation of blood through the heart and great vessels.

The first component, cardiac contraction and relaxation and the resulting change in the size and shape of the cardiac chambers, can now be studied by a specially adapted method of angiocardiography which adds a dynamic concept to the anatomic features which are the usual aims of this procedure.

The second main component of the cardiac function is the effect of contraction on the hemodynamics; that is, the effect of the heart movements on the velocity, course and distribution of the blood flow. These factors can be assessed by following the flow of the radiopaque substance during its passage through the heart and the great vessels. As in the evaluation of the heart contractions, the recording must be sufficiently continuous to reproduce in the pictures all the necessary phases. The time relationships are also utilized. These are determined by simultaneously recording the electrocardiogram.

The same angiocardiographic procedure is thus suitable for the evaluation of both main components of the cardiac function. Artificial, unphysiological conditions must not be created in the performance of this examination, if a correct physiological approach to the interpretation is to be made.

Studies of the hemodynamics, as shown by the intracardiac course of the contrast medium, must take account of three main factors, namely, the velocity, the course and the degree of opacification. The points to be noted are as follows:

(1) *Velocity* is measured by the first appearance of contrast material in previously nonopacified heart chambers. As the serial exposure frequency is known, the time required for the passage of contrast medium from one chamber to another can be determined. So too, the total duration of the opacification of a chamber can be determined.

(2) *Course* or direction of the circulation is determined by the order in which the heart cavities and vessels successively become opacified.

(3) *Opacification.* The degree or density of opacification adds a quantitative aspect to the two factors just discussed. The characteristic feature of the opacification of the normal heart is the progressive dilution that the opaque substance undergoes in its passage through the heart chambers, the lungs and the great vessels as it mixes with unopacified blood. An increase in the volume of blood between the site of injection and the site of observation causes a reduction in the concentration of

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opaque substance, while a decrease in the rate of flow results principally in a prolongation of opacification.

From the data yielded by angiocardiography, it may be possible to identify as the cause of an abnormal dilution pattern such factors as reduced cardiac output, an increased volume of blood in the heart and blood vessels or some alteration in the course of the circulation, as in the presence of abnormal shunts. For example in left to right intracardiac shunts two phenomena may occur in the right side of the heart which may give very different results though both are due to the abnormal course that blood takes through the shunt. There may be a "positive" effect or reopacification when the chamber from which the shunt originates contains contrast substance and its shunted blood increases the opacification of the chamber receiving the shunted blood. Or the effect may be of a "negative" sort when the chamber from which the shunt originates contains no contrast substance and its shunted blood dilutes the opacification of the opacified chamber receiving the nonopacified blood. Whether changes in opacity come as a result of abnormal pathways such as have just been discussed or whether changes in opacity result from the progressive dilution of the contrast substance that occurs in normal hearts, the degree of opacity in any given chamber at any given time can be estimated. It is an evaluation of the estimated opacity that permits one to apply quantitative methods to the study of the hemodynamics.

A common property of the three factors outlined above is the fact that they permit a graphic representation of their reciprocal relationships. Two of them, velocity and opacification, can be expressed in measureable units and thus drawn in a coordinate system. The third, the course of the blood flow, offers the anatomic base on which the two former purely functional factors can be plotted.

The number of photographs that may be made in a single angiocardiographic study, especially if a rapid exposure frequency is used, is large and awkward to handle. They offer a complexity of anatomical and functional features the separate components of which are difficult to interpret. For the purpose of practical evaluation, a graphic presentation of the hemodynamic factors, separately condensed in easily read curves on a chart, would have advantages which are fairly obvious and do not require detailed discussion. Suffice it to say that the method is particularly advantageous in demonstrating the presence of intracardiac shunts. It is also useful in determining circulation time.

The Method of Graphic Visualization

The graphic demonstration of the features to be found in the angiocardiogram aims to condense all the desired information into a single diagram. The method used is best explained by analyzing the charts reproduced in figures 1 through 7. The actual electrocardiogram of the patient is traced across the top of the diagram and each exposure is marked by a vertical line. The horizontal lines represent the six most important areas or structures traversed or passed by the contrast medium on its way through the heart and the great vessels. They are, in the normal successive order, the vena cava, the right atrium and ventricle, the pulmonary artery, the left atrium and ventricle and finally the aorta. The degree of opacification is estimated for each cavity in each exposure, the estimate being expressed on an arbitrary scale, 0 to 5, and accurately plotted by entering the determinations at corresponding height above the horizontal line of the graph and connecting the successive points by straight lines. The grey-toned area between this and the base line indicates both the occurrence of opacification in the different cavities and its varying intensity.

The reading and interpretation of the three factors bearing on the hemodynamics, namely, course, velocity and opacification, requires the use of both the vertical and the horizontal scales.

Course is read horizontally. By referring to the electrocardiogram at the top of the diagram, the order in which the cavities become opacified is determined. Divergences from the normal are directly revealed. *Velocity* is also read horizontally. This factor can be read from the graph by determining the number of vertical (exposure intervals) lines from left to right between the first appearance of opacification in the two or several cavities in question, and thus measured exactly if the exposure rate is known. As the opacification is referred to the actual electrocardiogram, the velocity can be expressed in terms of the number of complete or partial heart cycles or it can be expressed in absolute time units, if time is accurately shown on the electrocardiogram. *Opacification* and *Distribution* are evaluated by both the horizontal and vertical

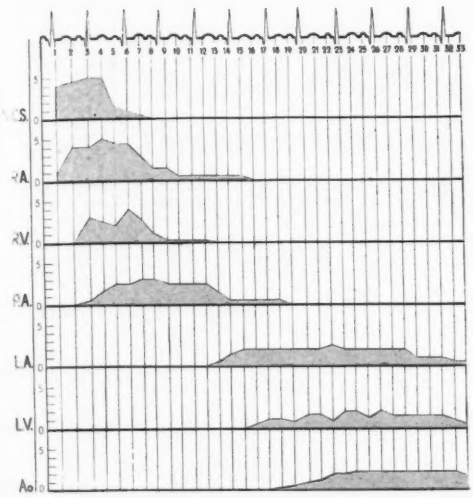

FIG. 1. *Normal Angiocardiogram.* The basic pattern of the normal angiocardiogram is well illustrated in this graph. A casual glance reveals the successive opacification of the different chambers and great vessels; each section is opacified a little later than the preceding one. The abrupt rise, high peak, and rapid decrease in concentration are striking in the right heart; less so on the left, since the contrast material is diluted in passing through the pulmonary circuit. The circulation time through the heart and lungs can be accurately determined, as regards both actual time and cardiac cycles.

V. C. When the contrast substance arrives at the caval orifice it maintains a high concentration for about one and one-half cardiac cycles and disappears shortly thereafter.

R. A. After a rapid opacification, a high concentration of contrast is maintained for two cardiac cycles, and at the end of the fifth cycle the right atrium is empty, just as the left atrium begins to fill.

R. V. The first atrial systole completely opacifies the right ventricle, as does the second, but by the time the left ventricle is visualized, the right is empty.

P. A. After the first right ventricular systole, the pulmonary artery has a high concentration of contrast substance which is maintained for three cycles. At the end of the fifth cycle the pulmonary artery is no longer visible.

L. A. The left atrium begins to fill just four cardiac cycles after the right atrium. The concentration rises and falls less abruptly and never reaches as high a level as on the right.

L. V. The first left atrial systole produces poor visualization of the ventricle, and only after the fourth cycle is maximal concentration obtained. This is the result of normal dilution in the pulmonary circulation.

Aorta The pattern is similar to that in the left ventricle, except, of course, that the contrast substance arrives one step later.

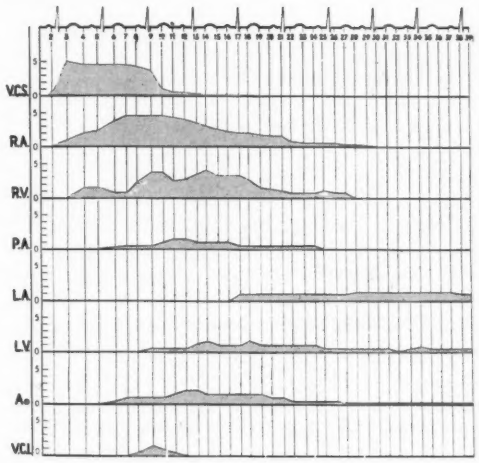

FIG. 2. *Tetralogy of Fallot.* This graph demonstrates three of the four features of the tetralogy of Fallot: 1. The pulmonic stenosis results in poor opacification of the pulmonary artery in spite of good concentration of contrast substance in the right ventricle; 2. the ventricular septal defect is indicated by early visualization of the left ventricle, before the left atrium; and 3. the overriding aorta is shown by premature opacification of the aorta, before the left heart is filled with contrast medium. Reflux into the inferior vena cava is a result of functional disturbance of the right atrium due to increased resistance to systolic emptying.

scales. The horizontal length of the grey-toned bed, indicating opacification, shows the length of time the contrast medium remains in a cavity. The height of the shaded area indicates the concentration and density of contrast medium and enables an approximate estimation of this relationship to be made.

Potentially Misleading Aspects of the Technic

As the graphic demonstration is based on determinations of roentgenographic densities, qualitative and quantitative, a correct interpretation requires that potentially misleading factors be avoided so far as possible. These may be caused by the method of opacification, by the technic used in injection and recording.

The opacification must not be influenced by variable and misleading extracardiac conditions. Therefore, the "basic" conditions during examina-

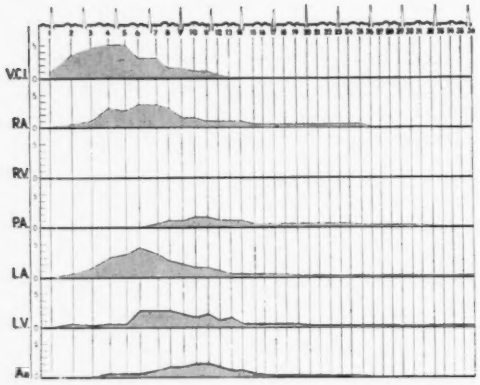

FIG. 3. *Tricuspid Atresia. Atrial Septal Defect with Right to Left Shunt and Patent Ductus Arteriosus.* Absence of opacification of the right ventricle indicates tricuspid atresia. The early visualization of the left heart results from the right to left shunt through an atrial septal defect. The pulmonary artery is opacified from the aorta by way of a patent ductus.

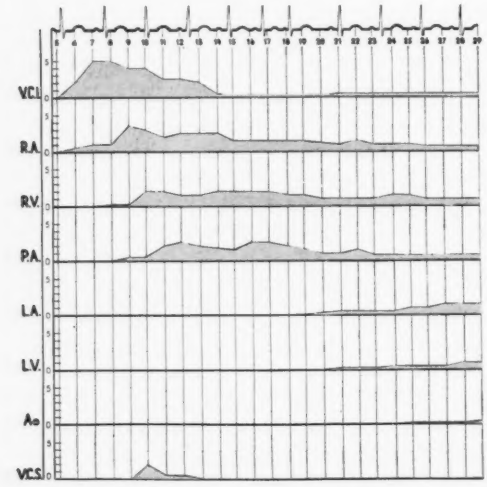

FIG. 4. *Isolated Pulmonic Stenosis, Prolonged Pulmonary Circulation Time.* The slow disappearance of contrast from the right heart is the result of inadequate emptying incident to pulmonic stenosis. Delayed visualization of the left heart rules out a right to left shunt through a septal defect associated with pulmonic stenosis and indicates prolonged pulmonary circulation time. There is a reflux into the superior vena cava. The poor opacification of the right ventricle is the result of dilution with an abnormally large quantity of residual blood because of inadequate emptying.

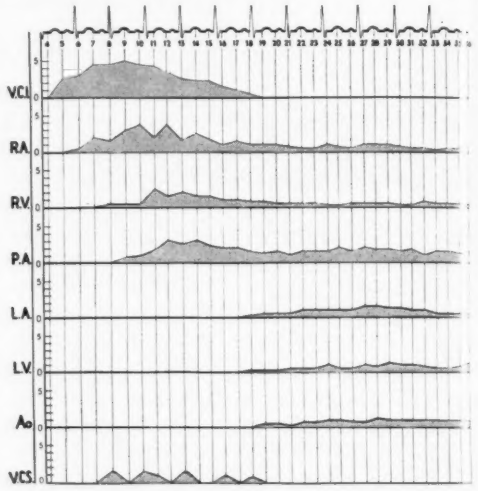

FIG. 5. *Atrial Septal Defect, Left to Right Shunt.* The prolonged opacification of the inferior vena cava may be the result of its greater distance from the site of injection to the heart. In spite of a high concentration in the vena cava, the right atrium is only moderately well opacified, indicating influx of non-opacified blood from the left atrium. A further indication of shunt is the fluctuation in the concentration of the contrast substance in the right atrium, with dilution occurring during atrial systole. The main dilution takes place in the right ventricle indicating that most of the shunted contrast medium passes from the left atrium directly down into this chamber without being considerably mixed with the contents of the right atrium. The prolonged opacification of all the chambers beyond the vena cava results from the short circuit through the atrial septal defect. Note the low concentration of contrast medium in the aorta. The atrial systolic reflux into the superior vena cava indicates a functional disturbance of the atrium. Coincident right to left shunt can be ruled out by the opacification of the left heart at approximately the normal time; in the presence of such a shunt the two atria would be visualized simultaneously.

tion must be uniform and comparable. It is well known that respiratory movements produce changes in the filling of the heart and the great vessels with resulting alterations in the apparent density of the contrast medium. The error introduced by deep and uneven breathing can be largely eliminated by the use of general anesthesia during the examination. In our series all children received 0.10 to 0.12 ml. per Kilogram of a 2.5 per cent solution of Avertin by rectum. During the sleep which resulted, respiration was even and shallow and introduced no error.

The second requirement is *uniform injection*

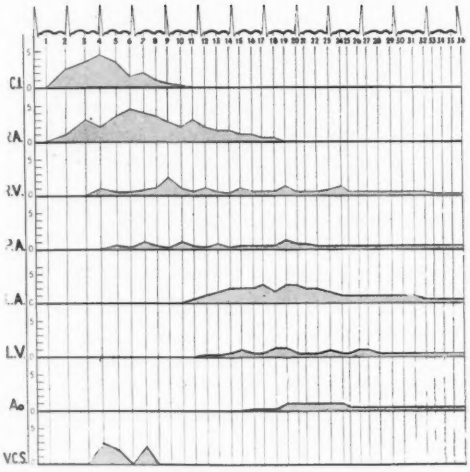

FIG. 6. *Ventricular Septal Defect, Left to Right Shunt.* As in the normal case, the chambers are opacified in successive steps. Superficial examination of the graph reveals the difference from the normal pattern, and the source of the shunt can be localized accurately in the ventricle.

The vena cava and right atrium are quickly opacified and rather promptly emptied, but the strikingly poor and prolonged opacification of the right ventricle and pulmonary artery contrasts sharply with the normal. Note the systolic-diastolic fluctuation in opacification in the right ventricle resulting from the variations in rate of flow through the defect. The pulmonary circulation time is not prolonged, and strangely enough, the left atrium seems better opacified than the right ventricle and pulmonary artery. Note the reflux into the superior vena cava.

technique and composition of the contrast medium. In all examinations we have used Umbradil in 70 per cent solution at a temperature of about 37 C. The injections have been given intravenously in a cubital or a malleolar vein. The amounts used are shown in table 1.

Satisfactory visualization of all heart chambers and the large vessels can usually be obtained with these amounts of contrast medium. The rate at which the material is injected has been kept constant as far as possible; cannulae of the same size have been used. In our opinion the injection of the contrast material into a vein at a considerable distance from the heart is less dangerous and causes less disturbance of the physiological conditions than an intracardiac injection.

The recording procedure whereby the length of exposure and the intervals between successive exposures are kept uniform for each case have been described in detail elsewhere. The more important steps follow. (1) Variations in exposure time are avoided by using an electronic timing device. (2)

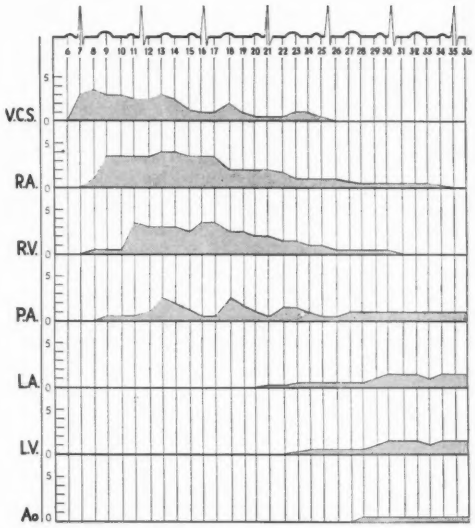

FIG. 7. *Patent Ductus, Left to Right Shunt.* The most striking feature of this graph is the systolic-diastolic variation of opacification in the pulmonary artery, the greatest concentration occurring at the end of ventricular systole and the dilution during ventricular diastole. Poor opacification of the left heart results from abnormal dilution of the contrast material in the pulmonary artery. The prolonged opacification of the right heart may be the result of functional disturbance, but in the pulmonary artery it is due to the shunt of opacified blood from the aorta.

Fluctuation of line voltage is prevented. (3) The angiocardiograms are taken in both the right and left anterior oblique projections simultaneously, at a rate of 10 to 12 exposures per second. (4) The time of each exposure is recorded on the simultaneously recorded electrocardiogram by an automatic marker connected to the control stand of the x-ray apparatus. (5) All the films are to be uniformly developed and processed.

The two oblique projections were used consistently. The determinations were made primarily from the right anterior oblique views since in this projection the atrium and ventricle do not overlap. However, by frequent reference to the left anterior oblique projections it was possible to ascertain when the contrast substance appeared in the left

TABLE 1.—*Amount of Contrast Media Used*

Weight in Kg	Dose in ml./Kg. of Weight	
	Injection in Cubital Vein	Injection in Malleolar Vein
2.5–5	1.00–1.5	1.25–1.50
5–10	1.00–1.25	1.25–1.50

heart. It is obviously more difficult to estimate accurately the degree of opacification in the left heart, but by frequent comparison of the two views, satisfactory results were obtained.

The *determination of the degree of opacification* was based on estimation of contrast density in the different pictures. After the presence of contrast medium was determined, the degree of density was subjectively estimated, and given a quantitative value based on a scale of density values of 0 to 5. Densitometric instrumental procedures were regarded as unsatisfactory. While the mixing of blood and contrast substance in the pulmonary artery and often in the right ventricle, and always in the left side of the heart would permit the use of this method, the uneven mixing of contrast medium and blood in the right side of the heart, especially the right atrium, results in a pattern of opacification too uneven for the practical use of densitometry. For this reason subjective estimation by a trained radiologist is believed to be the best method of arriving at a quantitative value for the density of opacification in each chamber in each exposure. All readings were made independently by two persons, one experienced in angiocardiography and one not. The resulting figures were averaged. In no case was there serious disagreement between the two sets of figures.

Discussion

The completed charts give an adequate diagrammatic representation of the phenomena of premature and prolonged opacification, re-opacification, dilution, and systolic-diastolic variation in opacification. In reading the graphs, each chamber should be judged concerning the time, duration and degree of opacification. Premature opacification, by which is meant, the appearance of the contrast substance in one chamber before it reaches the chamber whose opacification normally precedes it, is positive evidence of a right to left shunt into that chamber. Delayed opacification may indicate a proximal stenosis, and absence of opacification, atresia. Prolonged opacification or re-opacification of the right heart is presumably evidence of a left to right shunt, provided it is not due to the slow arrival of contrast substance through the vena cava. Left to right shunt is usually manifested by dilution of contrast substance and therefore lessening of the degree of opacification of the chamber which receives the shunted blood: this will often be accompanied by an abnormal systolic-diastolic variation in the degree of opacification. Functional disturbances of the right atrium may result in reflux into the vena cava into which no contrast substance was injected; hence both venae cavae are shown to have been opacified in some of the graphs.

Summary

This paper discusses the possibility of studying the cardiac movements and their relation to the resulting circulatory hemodynamics by biplane angiocardiography at a high exposure rate with synchronously recorded electrocardiograms. A method is described whereby the information yielded by this combination of studies can be put in the form of a simple, convenient graph. Graphs obtained from the study of subjects with normal and with abnormal hearts are presented to show how the data included in the graphs can be used to give important information concerning the structure and function of the heart.

Summario in Interlingua

Es discutite le possibilitate de studiar le movimentos cardiac e lor relation al resultante hemodynamica circulatori per medio de angiocardiographia biplan a alte frequentia de exposition con synchrone registrationes electrocardiographic. Un methodo es describite per que le information obtenite in un tal combination de studios pote esser colligite in le forma de un simple e commode graphico. Le autores presenta specimens de tal graphicos obtenite ab subjectos con normal e anormal cordes. Illos servi a demonstrar como le datos incorporate in iste genere de graphico pote esser usate pro revelar importante informationes in re le structura e le function del corde.

Electrolyte Studies in Heart Failure

I. Cellular Factors in the Pathogenesis of the Edema of Congestive Heart Failure

By Lloyd T. Iseri, M.D., Albert J. Boyle, M.D., Ph.D., Douglas E. Chandler, M.D. and Gordon B. Myers, M.D.

CIRCULATORY insufficiency in cardiac failure appears to produce changes in cellular metabolism, resulting in extrusion of certain cations out of the cells[1, 2, 3, 4] and in migration of water into the cells.[3, 4, 5, 6] These changes, presumably, follow activation of cellular base and an increase in cellular osmolarity.[3, 4, 7] Along with these intracellular alterations, the extracellular fluid tends to become hypertonic.[8]

The relationship between cellular and extracellular changes in the pathogenesis of congestive heart failure remains obscure, not only because of distortions produced by therapeutic factors,[8, 9] but also because of the fact that studies on the extracellular fluid have not been correlated with the degree or the trend of the circulatory failure at the time of the study.[10] The present report attempts to elucidate the cellular factors involved in the pathogenesis of the edema of congestive cardiac failure. The following data obtained from direct muscle analysis show potassium deficits in skeletal muscle during congestive failure and restitution with recovery.

Method and Material

Two muscle samples, weighing 0.25 to 0.50 Gm., were obtained with extreme care from the deltoid muscle of 10 patients shortly after their admission to the hospital in frank congestive heart failure. Regional block anesthesia was attained with 1 per cent procaine by infiltration of the skin at least 2.5 cm. away from the site of the biopsy. The muscle samples were rolled lightly and quickly over dry gauze and placed immediately into tared covered crucibles and weighed. One sample was heated to 100 C. for four to six hours, cooled in a desiccator and reweighed. This procedure was repeated until a constant dry weight was obtained. The sample was then digested with perchloric-nitric acid mixture and analyzed for potassium and sodium. The second sample was not heated to dry weight, but digested with strong sodium hydroxide and analyzed for chloride. Concurrent with muscle biopsy, plasma samples were obtained for determination of sodium, potassium and chloride levels.

These studies were then repeated 9 to 56 days later, well after restoration of cardiac compensation. Body weight, venous pressure, circulation time, and vital lung capacity were obtained periodically to follow the clinical progress of cardiac compensation. Five of the 10 patients received no mercurial injections. Four received one to two injections during the first five days of therapy, but none received any during the seven days preceding the second muscle biopsy. One patient (C. G.) required several mercurial injections during the four weeks before compensation, but received no injection during the next four weeks preceding the second muscle biopsy study.

Calculations of intracellular and extracellular distribution of water and potassium were made, utilizing the chloride content and the plasma chloride concentrations.[11] Corrections were made for the theoretical inactive chloride content of 1 mEq. per 100 Gm. of fat free tissue solids. The plasma chloride concentration was corrected for Donnan's effect and plasma water content by multiplying with 1.08. In view of the recent studies performed by Nichols and coworkers,[12] the chloride space corrected for the inactive intracellular moiety of Yannet and Darrow,[13] which would more than allow for the slightly higher concentration of chloride in connective tissue water, would appear to be the most accurate measure of the extracellular space. Tissue fat content was assumed to be 1 per cent. Since the muscle samples, by necessity, were small, it was not considered feasible to extract and analyze for fat; however, because of the smallness of the samples, it was relatively simple to obtain samples which contained no fascia or septum and hence only minimal quantities of fat.

Chemical Methods. Plasma sodium and potassium were analyzed on the flame photometer, according to the method previously described.[14] Plasma chloride

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This work was supported in part by grants from the Michigan Heart Association and the National Institute of Health (H-1471).

was determined either by polarographic[15] or by titration[16, 17] methods. Plasma carbon dioxide combining power was measured by vacuum extraction.[18] Tissue sodium and potassium were analyzed on the flame photometer after suitable preparation of the sample. Tissue chlorides were analyzed by microtitration, using Volhard's method.[16]

Results

The results of analyses of muscle tissue obtained during and after congestive heart failure and the derived values for distribution of water and potassium are given in table 1.

The average loss of weight in these 10 patients during the 9 to 56 day period of compensation was 16.8 Kg. and the range was from 5.32 to 26.90 Kg. The average venous pressure fell from 243 mm. H_2O to 112 mm. and the average circulation time (arm-to-tongue Decholin) decreased from 36 to 27 seconds.

During the height of congestive failure, the average water, potassium and chloride contents of muscle were 78.2 Gm., 5.81 mEq., and 3.53 mEq. per 100 Gm. of wet tissue, respectively. After compensation these values were 75.9 Gm., 8.33 mEq., and 2.52 mEq., respectively. The decrease in water content occurred in each of the 10 cases, although it was hardly significant in four of the cases. There was a significant increase in potassium content of muscle in eight cases, a slight increase in one, and an actual decrease in one. Eight of the 10 cases showed a decrease in the chloride content, but two cases showed an increase.

Calculations of extracellular and intracellular water content in terms of per cent of wet tissue revealed an average extracellular volume of 29.05 per cent and an average intracellular volume of 49.1 per cent during the height of failure, and 20.9 and 55.0 per cent, respectively, after compensation. Individually, the per cent of extracellular water per unit mass of wet tissue decreased in eight cases, but increased in two. As was to be expected from the minimal change occurring in total water, the change in intracellular water was

Table 1.—*Analysis of Muscle During Congestive Heart Failure and After Recovery*

Pt.	Sex	Age	Cardiac Diagnosis	Date of Study	Body Weight Kg.	V.P. mm. H_2O	C.T. Sec.	Plasma				Muscle Per 100 Gm. Tissue			Derived Values				
								Na mEq./L.	K mEq./L.	Cl mEq./L.	CO_2 mEq./L.	H_2O Gm.	K mEq.	Cl mEq.	ECW* %	ICW† %	ICW Per 100 Gm. F. F. S.§	ICK‡ Per 100 Gm. F. F. S.§	ICK mEq./L.
J. B.	M	69	Cor. P.	10/16	101.0	245	40	140	3.80	116.0	28	77.5	4.05	5.80	44.5	33.0	154	18.0	118
				11/ 1	74.9	150	28	140	3.90	107.0	23	73.0	7.35	3.90	31.5	41.5	164	27.8	174
W. W.	M	54	AHD	12/ 7	70.5	160	48	152	4.06	96.5	27	80.5	7.35	1.76	15.1	65.4	355	39.5	111
				12/24	51.8	68	30	139	4.05	98.5	26	79.5	7.57	2.07	17.7	61.8	315	38.5	122
C. R.	M	53	RHD	12/14	86.7	188	36	136	4.53	110.7	18	77.6	4.77	3.40	26.6	51.0	240	21.7	91
			AHD	12/29	72.4	75	18	137	4.45	106.7	23	71.5	6.15	2.18	16.6	54.9	200	22.5	111
A. K.	M	60	HHD	1/20	65.0	190	23	126	4.80	104.6	16	77.0	3.56	3.40	28.3	48.8	222	15.6	70
				2/ 5	49.8	52	18	130	4.47	97.6	16	76.4	7.68	4.09	36.7	39.7	176	33.3	189
C. G.	M	57	HHD	1/25	62.8	320	35	126	4.80	104.6	16	80.0	3.84	3.96	33.5	46.5	245	19.4	79
				3/21	51.0	182	38	140	4.31	96.5	18	78.9	7.39	3.11	28.0	50.9	253	36.0	144
P. P.	M	59	AHD	1/30	90.1	385	50	140	4.09	124.0	13	80.0	6.92	4.35	31.0	49.0	258	35.7	138
				2/12	66.0	142	40	125	4.87	115.8	21	76.0	5.65	2.70	19.8	56.2	245	24.1	99
J. A.	M	54	RHD	5/28	66.7	240	—	156	5.00	99.4	19	78.9	3.74	3.30	29.1	48.1	240	17.8	75
				6/ 5	61.4	140	—	146	5.00	91.9	26	76.0	8.29	2.55	23.5	52.5	228	35.5	156
E. G.	M	45	HHD	4/13	117.5	268	30	146	4.00	99.0	23	80.0	7.11	3.95	35.2	44.8	236	37.0	156
				5/22	90.6	165	25	140	5.28	110.5	16	79.0	10.20	1.49	10.8	68.2	341	50.8	149
B. L.	M	50	HHD	4/10	74.2	140	40	140	3.90	94.6	22	77.4	8.21	3.45	31.7	45.7	212	37.5	176
				4/19	67.9	90	31	140	4.64	102.6	17	75.2	13.30	1.39	10.5	64.7	283	58.0	205
D. H.	M	55	RHD	5/ 1	89.8	292	18	160	5.16	101.7	22	74.0	8.55	1.98	15.7	58.3	225	32.5	145
				5/15	70.6	54	15	144	4.11	101.0	21	73.5	9.76	1.77	13.9	59.6	233	38.0	162
Average				Decomp.	82.4	243	36	142	4.41	105.1	20	78.2	5.81	3.53	29.1	49.1	239	27.5	116
				Comp.	65.6	112	27	138	4.51	102.8	21	75.9	8.33	2.52	20.9	55.0	244	36.5	151

* Extracellular water.
† Intracellular water.
‡ Intracellular potassium.
§ Fat-free solids. Fat content assumed as 1%.

in the opposite direction to the change in the extracellular water.

The amount of intracellular water per 100 Gm. of "fat free" solids (fat content assumed to be 1 per cent of wet tissue) remained the same, averaging 239 Gm. during congestive failure and 244 Gm. after compensation, increasing in five and decreasing in five.

The intracellular potassium concentration increased from an average of 116 mEq. to an average of 151 mEq. per liter of intracellular water. Considerable variation was found in the actual potassium concentration during failure (range 74.5 to 176 mEq. per liter), but the trend with compensation was quite consistent, being increased in eight, unchanged in one, and decreased in one. Calculation of intracellular potassium content per 100 Gm. of tissue solids showed an increase from an average of 27.5 mEq. to an average of 36.5 mEq. There was an increase found in eight cases and a decrease in two.

Because of extreme variability in the results of sodium analysis, the data did not lend itself to any interpretation and hence are not presented.

Discussion

The results of the muscle biopsy studies clearly indicate a deficit of cellular potassium in congestive heart failure and a repletion after recovery, thereby substantiating the conclusions reached from indirect metabolic studies.[1-4] The magnitude of potassium deficit per unit mass of wet tissue (−30.1 per cent of total control content) was considerably greater than that obtained by Talso and associates[19] (−22.3 per cent) or by Mokotoff and colleagues[20] (−17.4 per cent) and could hardly be attributed to any difference in the extracellular or intracellular water content. The greater deficit of muscle potassium found in the present study may have been due to: (1) the fact that our comparisons were made on specimens from the same patient during the height of failure and after complete compensation, (2) the fact that these patients were studied immediately after admission to the hospital in profound and progressive congestive heart failure before any alleviation of the circulatory insufficiency, or (3) the fact that the muscle samples were obtained from the deltoid muscle rather than from the dependent muscles of the lower extremity, where hydrostatic pressure may influence not only the extracellular, but also the intracellular distribution of water and electrolytes.

In contrast to previous reports,[17, 18] the mean content of potassium per unit of tissue solids was significantly lower (−23.5 per cent) during cardiac failure than after compensation. Even though exact corrections could not be made for muscle fat, the increase in potassium content was too great to be explainable by a decrease in mean fat content. One would, moreover, expect an increase in mean fat content during recovery.

The deficit of potassium becomes more apparent after calculation of the concentration per liter of cell water. The mean value increased from 116 to 151 mEq. per liter. The intracellular potassium concentration during failure in this series was decidedly lower than in other reports,[17, 18] but the values after compensation were comparable.

The total water per unit of wet tissue was greater during cardiac decompensation than during compensation, although the percentile difference from the control (3 per cent) was less than that found by either Talso and coworkers (6.0 per cent)[19] or Mokotoff and associates (9.5 per cent).[20] The less marked difference in total water content was undoubtedly due to the fact that the muscle samples were obtained from areas not subjected to the hydrostatic collection of edema fluid. Nevertheless, the calculated mean extracellular water was increased during congestive failure by 43 per cent over the control period. This was comparable to the 48 per cent increase found by Talso and colleagues,[19] but less than the 88 per cent increase found by Mokotoff.[20] The intracellular water per unit of wet tissue was decreased and the calculated cellular water in terms of tissue solids was essentially the same before and after compensation. Mokotoff and coworkers[20] also failed to demonstrate any significant change in intracellular water per unit of fat-free tissue solids; however, since there is little reason to believe that the quan-

tity of fat-free solids per unit number of cells will remain the same in such a profound physiological disturbance as cardiac failure, one cannot rule out the possibility that the cells may be overhydrated in congestive heart failure. It is entirely possible for a given mass of tissue to have the same amount of solids and yet have less cells. If this were so, the cells would be overladen with water in spite of the finding that intracellular water per unit of fat-free solids was no different in congestive failure than in the controls. In fact, the studies by Talso and associates[19] actually demonstrated an increase of cell water in terms of fat free solids in congestive failure.

These muscle studies thus indicate a significant decrease in the concentration of intracellular potassium in congestive failure, whether it be by loss of potassium, by increase of cell water, or by both. This decrease in intracellular potassium concentration can be explained by osmotic activation of intracellular base, which forces potassium out of the cells and/or absorbs water into the cells. In this regard, it has been shown by direct means that intracellular muscle sodium is also decreased in the cells.[19] It is obvious that precise studies of the extracellular compartment would be necessary to clarify the nature of the changes occurring within the cells. These studies will be reported in a later paper.[21]

Summary

Muscle analyses for water, potassium, and chloride were made in 10 cardiac patients during and after congestive heart failure. The potassium content per unit of wet tissue during failure was 30.1 per cent less than that during compensation. The concentration of potassium in the intracellular water increased from 116 mEq. per liter to 151 mEq. per liter with compensation. Calculated extracellular water decreased, but no change in intracellular water per unit of tissue solids was found.

Summario in Interlingua

Specimens bioptic de musculo esseva analysate pro aqua, kalium, e chlorido in 10 patientes cardiac durante e post congestive insufficientia cardiac. Le contento de kalium per unitate de texito non-desiccate esseva 30,1 pro cento minus que le contento de kalium durante compensation. Le concentration de kalium in le aqua intracellular accresceva per le compensation ab 116 mEq per litro a 151 mEq per litro. Le calculate valores de aqua extracellular decresceva, sed nulle cambiamento esseva constatate in le quantitate de aqua intracellular per unitate de solidos texital.

Acknowledgment

We wish to express our appreciation to Dr. Ivan J. Mader, Miss Irene Parker, R.N., Mrs. Leona de Marky and Miss Vivian Kapuscinski for their invaluable assistance in this study.

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Electrolyte Studies in Heart Failure

II. Extracellular Factors in the Pathogenesis of Congestive Edema

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Indirect metabolic studies and direct muscle biopsy studies have indicated diminution of intracellular electrolyte concentration during congestive heart failure explainable by extrusion of these electrolytes due to increase in osmolarity within the cells. Acute and chronic physical and circulatory stress in cardiac patients produced an elevation of plasma sodium concentration indicative of a concomittant increase in osmolarity of the extracellular fluid.

PREVIOUS studies indicate the possibility of an intrinsic rise in intracellular osmolarity during congestive heart failure[1-3] to explain the decrease in intracellular potassium concentration[1-3] and the shift of water into the cells.[1, 2, 7, 9, 10] Expansion of the extracellular fluid space is characteristic of congestive heart failure, but the exact composition of this fluid, especially during the development of failure, has not been adequately investigated.[11-13] If the intracellular fluid becomes hypertonic from circulatory insufficiency, the extracellular fluid should also become hypertonic in order to maintain equilibrium between the two phases.[13]

The following study, carried out in cardiac patients, shows an obligatory rise in plasma sodium concentration following acute and chronic physical stress.

Method and Material

I. *Plasma Electrolyte Studies Following Acute Activity.* The effect of acute circulatory stress on plasma electrolytes was studied 10 times in 9 cardiac patients who were admitted in, or induced into, a state of decompensation. Duplicate plasma sodium, potassium, and chloride determinations were first made during the resting and fasting period. The patients were then given 4.0 Gm. of sodium chloride in 300 ml. of water orally and after one hour of rest were subjected to physical stress. In eight experiments the Master two-step test was used and in two a slow level walk of 10 to 15 minutes was employed. Soon after the physical activity, plasma samples for electrolyte determinations were again obtained. The venous pressure and circulation time were measured before and after exercise in eight experiments. The degree of dyspnea was estimated after each exercise.

The same studies were also made during the state of cardiac compensation in four cases. At no time was the amount of work performed during the compensated state less than the work performed during the state of decompensation.

Similar studies were performed on four fasting normal subjects, who were given 4.0 Gm. of sodium chloride in 300 c.c. of water orally and subjected to the Master two-step exercise. The resting electrolytes were obtained one hour after ingestion of the sodium chloride. Subject P. E. undertook 36 complete circuits over the stairs rather rapidly and was noticeably dyspneic at the time of the second sampling of blood. The other three normal subjects completed 15 circuits over the stairs and were only slightly dyspneic.

II. *Plasma Electrolyte Studies Following Chronic Diurnal Activity.* In this study plasma electrolyte concentrations were measured in seven cardiac patients early in the morning before any physical activity and again immediately before retiring after a day of unrestricted diet (approximately 90 mEq. sodium) and physical activity. These studies were conducted when the patients were steadily gaining weight and having increasing symptoms of dyspnea and orthopnea from progressive congestive failure for at least three days before the test. The venous pressure and circulation time were measured in five patients in the morning and again at night along with the plasma electrolytes. Body weight was measured in each patient on the Troemmer beam balance.

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This work was supported in part by grants from the Michigan Heart Association and the National Institutes of Health (H-1471).

III. *Chemical Methods.* The methods used in these studies have been described in the preceding paper.[8]

Results

I. *Effect of Acute Circulatory Stress*

During the period of progressive congestive failure, a sodium chloride load, followed an hour later by acute physical stress, resulted in a significant rise in the plasma sodium concentration in six separate experiments performed on five patients (table 1). The average rise was 5.7 mEq. per liter and the range was 3.3 to 7.6 mEq. per liter. The magnitude of this rise was significantly greater than the variations found in the duplicate analyses (average deviation, ±0.6 mEq. per liter, range ±0.0 to ±1.9 mEq. per liter). Two to 3-plus dyspnea was elicited in each instance and the venous pressure was increased significantly in the five patients in whom it was measured. As was to be expected, the circulation time usually decreased. Patient B. T., who was admitted in severe congestive failure, showed the maximum increase in plasma sodium concentration, even after a maximally tolerable exercise of only three complete circuits on the two-step stairs. Twelve days later, after partial compensation of cardiac function, the patient was able to tolerate seven complete circuits on the two-step stairs; however, he became moderately dyspneic. The plasma sodium concentration rose by 6.2 mEq. per liter. Patient M. F., who showed moderate dyspnea and a rise of 3.3 mEq. per liter after 15 minutes of level walking, showed no change in the plasma sodium level one hour after salt load or after five minutes of level walking. Three other patients and four separate subjects showed no increase in plasma sodium concentration with only the salt load. Two patients showed only a minimal rise in plasma sodium concentration with exercise. Patient M. H., with a rise of only 1.6 mEq. per liter, was subjected to five minutes of slow level walking. Dyspnea was not noted. Patient A. K. was induced into a state of mild decompensation by liberal dietary salt intake for 12 days. During this period there was a weight gain of only 1.55 Kg. and no development of peripheral edema or rise in venous pressure. Although this patient was subjected to moderately strenuous physical stress, there was no provocation of significant dyspnea or rise in venous pressure. The plasma sodium rose a mere 2.0 mEq. per liter. Two patients showed no rise in plasma sodium level after exercise. E. W. had an abnormally high sodium level, to begin with, and in spite of the development of moderate dyspnea, following exercise, the plasma sodium concentration remained essentially the same. Significantly, the venous pressure fell in this patient. Patient W. W. also showed no elevation in the plasma sodium level. Dyspnea was minimal and the venous pressure actually decreased significantly.

No significant or consistent change was noted in the plasma potassium, chloride, or carbon dioxide combining power before or after the physical stress in decompensated patients. These studies were also performed during a state of compensation in four patients. The physical work carried out by these patients was equal to the work which they performed at the time of failure and consequently much less than their tolerable limit after they had compensated. As can be seen in table 1, the plasma electrolyte concentrations, including the plasma sodium level, did not change significantly. Patient B. T., after full cardiac compensation and evacuation of 9.3 Kg. of excess body fluid, was subjected to the same amount of work (three complete circuits on the two-step stairs) as during frank congestive failure. There was no dyspnea, rise in venous pressure, or rise in plasma sodium concentration.

Three of the four normal subjects showed an increase in plasma sodium concentration, following acute physical stress (table 2). Subject P. E., who showed the greatest rise, 5.1 mEq. per liter, completed 36 circuits over the Master two-step stairs and was noticeably dyspneic. The other two subjects showed a slight rise in plasma sodium concentration upon completing fifteen circuits and were mildly dyspneic.

II. *Effect of Chronic Activity on the Plasma Electrolytes*

Six cardiac patients, who were gaining weight slowly from congestive failure, induced by

TABLE 1.—*Plasma Electrolyte Changes in Cardiac Patients Following Acute Physical Stress*

No.	Patient	Experimental Condition*	Decompensated								Compensated							
			Wt. Kg.	V. P. mm.	C. T. sec.	Dyspnea	Plasma Electrolytes mEq./L. Na	K	Cl	CO_2	Wt. Kg.	V. P. mm.	C. T. sec.	Dyspnea	Plasma Electrolytes mEq./L. Na	K	Cl	CO_2
1	J. H. 52 M. Hypert.	Rest Stress† Diff.	150 — —	92 170 +78	20 18 −2	+ ++	146.3 ± 0.7 151.2 ± 0.0 +4.8	3.74 ± .10 4.18 ± .00 +.44	101.3 ± 0.5 102.8 ± 0.3 +1.5	26.3 20.4 −5.9	140 — —	120 86 −34	25 18 −7	0 0	151.0 ± 0.7 150.6 ± 1.3 −0.4	3.88 ± .13 3.83 ± .07 −.05	101.3 ± 0.3 98.4 ± 0.4 −2.7	20.4 21.8 +1.4
2	W. W. 66 M. Hypert.	Rest Stress† Diff.	89.2	185 210 +25	33 27 −6	+ +++	140.0 ± 0.0 146.5 ± 6.5 +6.5	3.84 ± .01 3.83 ± .05 −.01	110.0 ± 0.3 108.5 ± 0.3 −1.5	14.5 14.5 0	88.6 — —	194 194 0	20 21 +1	0 0	140.0 ± 0.0 140.0 ± 0.0 0	4.22 ± .01 4.44 ± .00 +0.22	100.5 ± 0.6 102.1 ± 0.1 +1.6	14.8 13.2 −1.6
3	B. T. 51 M Rheum.	Rest Stress† Diff.	84.5 — —	138 185 +47	30 32 +2	0 ++	141.0 ± 1.0 148.6 ± 1.2 +7.6	3.68 ± .05 3.49 ± .04 −.19	96.7 ± 0.7 102.8 ± 0.4 +6.1	25.0 25.0 0	75.2 — —	96 98 +2	31 26 −5	0 0	150.1 ± 0.7 148.8 ± 0.7 −1.3	4.84 ± .03 4.45 ± .02 −.39	98.2 ± 0.2 96.7 ± 0.2 −1.5	17.5 22.8 +5.3
4	B. T.‡	Rest Stress† Diff.	77.2 — —	102 112 +10	40 23 −17	0 +++	145.8 ± 0.0 152.0 ± 0.9 +6.2	4.82 ± .00 5.29 ± .01 +.47	99.4 ± 0.2 96.2 ± 0.2 −3.2	21.4 17.9 −4.5								
5	D. G. 51 F. Rheum.	Rest 1 hr. after salt Stress† Diff.	54.4 — — —	226 230 233 +7	37 — 23 −14	0 0 ++	152.5 ± 0.5 153.5 ± 1.5 158.0 ± 0.0 +5.5	4.63 ± .04 4.52 ± .02 4.82 ± .03 +.19										
6	M. F. 58 F. Hypert.	Rest 1 hr. after salt Stress‡ Diff.	111.2 — — —	238 — — —	23 — — —	0 0 ++	155.7 ± 1.5 156.3 ± 0.1 159.0 ± 0.0 +3.3	5.53 ± .07 5.45 ± .03 5.60 ± .03 +.07	103.7 ± 1.1 107.1 ± 0.5 103.9 ± 0.8 +0.2	— — — —								
7	M. H. 52 F. Rheum.	Rest Stress‡ Diff.	58.9 — —	— 246 —	— 55 —	0 0	138.4 ± 0.5 140.0 ± 0.0 +1.6	4.18 ± .01 4.25 ± .23 +.07	108.5 − 109.1 ± 0.2 +0.6	— —	55.0	130 190 +60	45 35 −10	0 0	137.6 ± 0.0 137.4 ± 1.9 −0.2	3.68 ± .11 3.85 ± .00 +.17	104.6 − 103.6 ± 0.2 −1.0	— —
8	A. K. 60 M. Arterioscl.	Rest Stress† Diff.	51.0	60 63 +3	17 17 0	0 +	141.5 ± 1.5 143.5 ± 0.5 +2.0	4.62 ± .39 4.22 ± .02 −.40	101.6 ± 3.1 100.1 ± 0.4 −1.5	22.6 22.6 0								
9	E. W. 60 M. Luetic	Rest 1 hr. after salt Stress† Diff.	75.9	260 204 216 −44	64 67 58 −6	0 0 ++	163.0 ± 1.0 160.5 ± 0.5 162.5 ± 0.5 −0.5	6.38 ± .00 6.55 ± .05 6.40 ± .05 +.02										
10	W. W. 50 M. Malig. Hypert.	Rest 1 hr. after salt Stress† Diff.	93.0	164 — 133 −31	28 — 24 −4	0 0 +	150.0 ± 0.0 148.8 ± 1.3 149.0 ± 1.0 −1.0	3.96 ± .03 4.08 ± .03 3.85 ± .05 −.11										

* Each patient ingested 4 Gm. NaCl in 300 ml. water after rest.
† Three to 10 complete circuits on Master's two-step test.
‡ Ten to 15 minutes of level walk.

TABLE 2.—*Plasma Electrolyte Changes in Normal Subjects Following Acute Physical Stress*

No.	Subj.	Experiment Condition*	V. P. mm. H_2O	C. T. sec.	Degree Dysp.	Plasma Electrolytes mEq./L.		Hct.
						Na	K	
1	P. E.	Resting	83	12	0	152.9 ± 1.1	4.35 ± 0.04	48.1
		Master's 36×	95	13	+	158.0 ± 0.5	4.68 ± 0.08	48.3
		Difference	+12	+1		+5.1	+0.33	+0.2
2	R. O.	Resting	90	17	0	156.9 ± 1.5	4.38 ± 0.07	54.1
		Master's 15×	135	23	0	155.8 ± 0.5	4.69 ± 0.01	54.1
		Difference	+45	+6		−1.1	+0.31	+0.0
3	S. P.	Resting	90	13	0	155.3 ± 0.0	3.99 ± 0.06	48.1
		Master's 15×	78	16	0	159.1 ± 0.6	4.21 ± 0.00	48.1
		Difference	−12	+3		+3.8	+0.22	+0.0
4	T. R.	Resting	82	13	0	154.2 ± 1.1	5.04 ± 0.03	54.1
		Master's 15×	130	15	0	156.9 ± 0.7	4.91 ± 0.04	54.8
		Difference	+48	+2		+2.7	−0.13	+0.7

* Each subject ingested 4 Gm. NaCl in 300 ml. one hour before experiment.

unrestricted activity and dietary sodium intake, showed a diurnal rise in plasma sodium concentration, averaging 4.7 mEq. per liter and ranging from 2.0 to 8.4 mEq. per liter (table 3). There was an average weight gain of 1.71 Kg. during the day. Much of the diurnal weight gain was lost during the night, but the increment lost was less than the gain during the day, so that a progressive weight increase occurred from day to day. The venous pressures rose significantly in two patients and remained essentially unchanged in three others. There was no consistent change in the plasma potassium or chloride concentration between the early morning resting and the late evening postactivity periods.

One patient with diabetes mellitus and intercapillary glomerulosclerosis showed a reversal of the above trend, but because of heavy lipemia of the evening plasma, this was to be expected, in view of the recent study by Albrink, Hald and Man,[14] who showed that the water content of lipemic sera is greatly reduced. If the water content in this patient's plasma had decreased from 95 per cent to 90 per cent, the corrected sodium concentration would have increased by 4 mEq., from 153 to 157 mEq. per liter of water.

DISCUSSION

These studies, conducted on plasma electrolytes during progressive cardiac failure, revealed a rise in the sodium concentration, following both acute and chronic physical stress. The rise was greater than the maximum deviation from the average of duplicate analyses in all but two cases. The increase found after acute stress was not due to the salt load administered one hour previously, as indicated by the absence of any change in four patients studied during compensation and in four patients and four subjects who had plasma samples drawn one hour after the salt load. There appeared to be some correlation between the degree of rise in the plasma sodium level and the degree of dyspnea produced by the circulatory stress, but the number of cases studied is too small for a definite conclusion. Two patients showed no rise in plasma sodium level following exercise, probably because of an initially high level in one (E. W.) and because of insufficient circulatory stress, as indicated by an actual decrease in the venous pressure in the other (W. W.).

Apparently an elevation of plasma sodium can be produced in the normal subjects as well, so that the response of the cardiac patients may be merely a quantitative, rather than a qualitative, difference. Comparable studies, such as these, have not been reported; however, Newman and his associates[15, 4] have shown a decrease in sodium excretion from increased tubular reabsorption, following mild exercise in the cardiac and moderate exercise in the

† Three to 10 complete circuits on Master's two-step test.
‡ Ten to 15 minutes of level walk.

TABLE 3.—*Diurnal Plasma Electrolyte Changes in Decompensated Cardiac Patients*

No.	Patient	Age	Sex	Type of Heart Disease	Time Day	Wt. Kg.	V. P. mm. H_2O	C. T. sec.	Plasma Electrolytes mEq./L.		
									Na	K	Cl
1	J. B.	55	M	Cor. Pulm.	A. M.	62.78	—	—	141.1 ± 1.0	5.10 ± 0.00	100.4.±.0.0
					P. M.	63.48	—	—	149.5 ± 1.0	4.94 ± 0.02	101.0 ± 0.0
						+0.70	—	—	+8.4	−.16	+0.6
2	N. D.	61	M	A.S.H.D.	A. M.	63.22	124	23	147.4 ± 0.7	4.16 ± 0.02	103.3 ± 0.8
				Cor. Pulm.	P. M.	65.67	154	22	149.5 ± 0.0	4.10 ± 0.00	106.6 ± 1.0
						+2.45	+30	−1	+2.1	−.06	+3.3
3	S. S.	42	F	H. H. D.	A. M.	58.96	320	65	146.0 ± 0.0	4.85 ± 0.06	118.9 ± 2.0
					P. M.	61.77	346	71	148.0 ± 0.0	4.78 ± 0.01	119.9 ± 0.5
						+2.81	+26	+6	+2.0	−.07	+1.0
4	S. B.	47	M	A. H. D.	A. M.	56.76	142	19	140.8 ± 0.8	3.75 ± 0.03	102.5 ± 0.0
				Cor. Pulm.	P. M.	58.53	148	18	146.6 ± 0.4	4.35 ± 0.01	94.1 ± 1.4
						+1.77	+6	−1	+5.8	+.60	−8.4
5	G. T.	36	F	R. H. D.	A. M.	76.75	147	21	140.0 ± 0.0	4.67 ± 0.03	116.5 ± 0.3
					P. M.	77.98	152	24	146.6 ± 0.3	4.33 ± 0.02	112.2 ± 1.5
						+1.23	+5	+3	+6.6	−.34	−4.3
6	P. P.	61	M	A. H. D.	A. M.	77.95	265	50	151.8 ± 0.4	4.14 ± 0.00	118.9 ± 0.6
				H. H. D.	P. M.	79.30	270	50	154.8 ± 0.0	4.21 ± 0.03	111.1 ± 0.5
						+1.35	+5	0	+3.0	+.07	−7.8
7	A. L.	62	F	Diabetes Intercap. Glom. Scl.	A. M.	59.21	—	—	145.3 ± 0.0	3.89 ± 0.00	110.1 ± 0.5
				A. H. D.	P. M.	61.71	—	—	141.4 ± 0.0*	4.30 ± 0.02*	104.8 ± 0.5*
						+2.50			−3.9	+.41	−5.3

* Markedly lipemic plasma.

normal subject. Plasma sodium level was not discussed in cardiac,[4] but apparently was not altered in normal subjects.[15] Since the blood lactic acid level, at least in the normal subjects, did not increase, these authors felt that anaerobic muscle work was not necessary to elicit renal tubular retention of sodium. This is in keeping with the observation that acute anoxia, per se, is not responsible for sodium retention.[15] Presumably the decrease in sodium excretion and proportionately less marked antidiuresis of water may partly explain the changes reflected in the plasma. On the other hand, the rapidity of plasma changes after acute exercise suggests the possibility of mass movement of water into, and/or of sodium out of, the cells. Rapid movements of water between intra- and extracellular compartments have been demonstrated indirectly by Welt and his associates in their study of patients undergoing shock therapy.[17] These authors suggest an increased intracellular osmolarity to explain the rise in plasma sodium concentrations. Studies with radioactive sodium have demonstrated that there is a continuous intra- and extracellular exchange of sodium.[18] Disproportionate interchange in either direction will, of course, alter the concentration of sodium in the two compartments. In vitro studies also suggest the possibility of the red blood cells as the source of plasma sodium.[19] The minute quantities of sodium found in the erythrocyte, however, make it unlikely that the rise in plasma sodium concentration in cardiac patients could be attributed entirely to shift of sodium out of the red blood cells into the entire extracellular space. Whether or not bone contributes to the extracellular sodium cannot be determined, but this source of supply must certainly be considered.[20, 21] Release of sodium from bone, red blood cells, or tissue cells will, in effect, be the same as increased tubular reabsorption of sodium in that sodium will be made available to the extracellular space.

Since measurements were not made of plasma or extracellular volume, it is impossible to determine whether or not water moved out of these compartments during circulatory stress. In four of the cardiac patients subjected to physical stress, a slight increase in the hematocrit value occurred, suggesting a slight shrinkage of the blood volume. Whatever the mechanism, the rise in plasma sodium concentration is compatible with the hypothesis that osmolarity of cellular fluid is increased during cardiac insufficiency.

Diametrically opposite conclusions reached from metabolic studies by Lusk and Palmer[22] cannot be commented upon in view of the fact that stools were not analyzed and that changes in extracellular volume were considered to be equal to changes in total body weight.

Simple hypo-osmotic dilution of extracellular fluids, postulated by Talso,[7] and the primary retention of water, suggested by Miller,[10] do not appear to be integral factors in the pathogenesis of congestive heart failure, in view of the finding that the plasma sodium concentration is increased, following physical exertion.

Any tentative schema for the pathogenesis of congestive failure must take into consideration the period of circulatory stress and the period of metabolic restitution.[23] It can be postulated from studies to date that during the circulatory stress imposed by physical activity, the body cells undergo certain metabolic changes which result in activation of the osmotically "bound" or inactive base.[1, 2, 3, 13] This would result in hyperosmolarity of the cells and, temporarily, a relative hypo-osmolarity of the extracellular fluid. As a consequence, water enters the cell and/or the freely movable electrolytes, such as sodium and potassium, emerge from the cells.* In order to further readjust for the inequilibrium, the kidney tubules retain sodium, presumably for the purpose of raising the osmolarity of the extracellular fluid, and also retain water to dilute the intracellular compartment. The humoral factor responsible for the retention of sodium is most likely released by the adrenal cortex,[24, 25] and is probably aldosterone (electrocortin).[26] The factor responsible for the retention of water may very well be the antidiuretic hormone.[27] Whether increased osmolarity within the cell, per se, rise in plasma sodium concentration, or the tendency for the extracellular space to temporarily decrease is responsible for antidiuretic activity remains to be seen.

* Preliminary studies indicate that magnesium does not emerge from the cells in cardiac failure.

The fact that the extracellular and blood volume is increased in edematous cardiac patients does not detract from the last possibility, since the predicted change during physical stress will be a slight decrease in the extracellular space. In this respect, the concept of a "volume receptor"[28] or "quantometer"[22] can be applied to the hypothesis set forth in this paper. The potassium element is lost rapidly into the urine as it emerges out of the cells, either because of limited ability of the kidney tubules to conserve potassium or because of the adrenal cortical activity.

It is probable that the changes outlined above occur in the normal as well as in the cardiac patients subjected to physical stress beyond their circulatory capacity. It is also probable that the normal subject undergoes certain metabolic adjustments, even while under continued stress,[29] so as to prevent progression or even to produce restitution of the cellular and extracellular changes. The patient with circulatory insufficiency will be limited in his adaptation to continued stress.

Up to this point, the schema accounts for the retention of sodium and water and loss of potassium, but does not explain the localization of the retained water in the extracellular space, which is characteristic of cardiac edema. These changes must take place during rest.

During rest the metabolic activity of the cells becomes normal and their intrinsic osmolarity is reduced. This allows for extrusion of water and uptake of potassium and small amounts of sodium. Since the extracellular space is interposed between the cell and the external environment, elimination of water by the cells will first tend to expand the extracellular space. In the compensated cardiac patient and in the normal subject, adequate rest will allow complete elimination of water and sodium which had been retained during stress. On the other hand, if cardio-renal hemodynamics are markedly abnormal, elimination of water and sodium will be incomplete and edema will develop.[30, 31] Moreover, if rest is inadequate or if the cardiac status is so impaired that rest cannot be fully attained, then there will be partial or incomplete correction of the intracellular balance and incomplete elimination of water and sodium from the extracellular space, producing the classical picture of congestive heart failure with its intracellular and extracellular derangements.

Summary

Variations in the plasma electrolyte concentrations were studied in 10 decompensated cardiac patients before and after physical stress and in six patients during the normal course of diurnal activity. Significant rise in the plasma sodium concentration was found, indicating an elevation of extracellular osmolarity. This was interpreted to reflect a rise in intracellular osmolarity. The pathogenesis of congestive heart failure is discussed in the light of these findings.

Summario in Interlingua

Esseva studiate variationes in le concentration de electrolytos plasmatic in 10 discompensate patientes cardiac ante e post un stress physic e in sex patientes in le curso normal de lor activitates diurne. Un significative augmento in le concentration del natrium plasmatic esseva constatate. Isto indica un elevation del osmolaritate extracellular. Le pathogenese de congestive insufficientia cardiac es discutite in le lumine de iste constatationes.

Acknowledgment

The authors wish to thank Dr. Clayton Shors, Dr. David Young, Mrs. Maxine Adams, Mrs. Nancy Davenport and Miss Irene Parker, R.N. for their invaluable clinical, technical and nursing assistance related to these studies.

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Effects of Hemorrhagic Shock on the Heart and Circulation of Intact Dogs

By DONALD B. HACKEL, M.D. AND WALTER T. GOODALE, M.D.

The metabolic, hemodynamic and pathologic effects of hemorrhagic shock on the hearts of intact dogs have been studied, using the technique of venous catheterization of the coronary sinus. Metabolic studies demonstrated an alteration in the pattern of myocardial carbohydrate metabolism during shock and evidence for a relative myocardial oxygen deficiency. Subendocardial hemorrhage or necrosis was found in the left ventricles of some of the dogs.

EVIDENCE that terminal circulatory failure in hemorrhagic shock in dogs may be due to myocardial depression comes from three general sources: 1. from physiologic analysis of central venous pressure, left auricular pressure, cardiac output, ventricular pressure curves and electrocardiograms by Sarnoff and associates,[1] Wiggers and his colleagues[2] and others; 2. from *in vitro* biochemical demonstrations of an altered myocardial carbohydrate metabolic pattern of animals in shock, such as those reported by Burdette[3]; 3. from pathological studies showing foci of myocardial damage in dogs killed at intervals after induction of various types of shock.[4]

The present experiments employ our previously reported coronary venous catheterization technique for studying coronary blood flow and myocardial metabolism in intact dogs.[5] This approach permits the measurement of both cardiodynamic and biochemical events *in vivo*, and their correlation with pathological changes.

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This work was done, in part, during the tenure of a Research Fellowship of the American Heart Association (D. B. H.) and was supported by a Research Grant (H-863) from the National Heart Institute of the National Institutes of Health, Public Health Service.

Presented in part before the 38th Annual Meeting of the Federation of American Societies for Experimental Biology, held in Atlantic City, N. J., April 14, 1954.

METHODS

Twelve normal mongrel dogs were anesthetized with a mixture of Nembutal and Dial-Urethane,* following morphine premedication (3 mg. per kilogram). Each animal was given streptomycin (200,000 U) and aqueous penicillin (200,000 U) intramuscularly and heparin (2.5 mg. per kilogram) by intravenous route. The coronary sinus and pulmonary artery were catheterized under fluoroscopic control, and a third catheter was placed in the aorta via the femoral artery. Left ventricular coronary blood flow was measured over a ten minute period by the nitrous oxide desaturation technique.[6] Coronary arterial and venous samples were also drawn during this period, enabling the simultaneous measurement of myocardial oxygen, lactate, pyruvate and glucose utilization. Cardiac output was calculated by the Fick principle with oxygen; blood pressures were recorded with a Sanborn electromanometer. Left ventricular work and efficiency could thus be calculated. The description of these procedures and the calculations employed have been given in detail in previous reports.[6,7] Serial electrocardiograms were obtained with a Sanborn Visocardiette.

The dogs were then bled from the femoral artery in stepwise fashion, 50 to 100 ml. at a time, until the blood pressure decreased from the control mean of 121.2 ± 4.5 to 54.3 ± 2.3 mm. Hg. This procedure took 45 to 60 minutes and required the withdrawal of blood equal to about 3.4 per cent of the body weight. A second set of determinations similar to those described above were then carried out. At this point hypotension was reversible, and reinfusion of blood resulted in an immediate proportional increase in arterial pressure levels. In nine of the dogs the blood pressure was maintained at 40 to 50 mm. Hg for the next three hours by repeated small withdrawals of blood, averaging 0.9 per cent of body weight. A third set of similar determinations were then performed. The blood that had been removed was returned and the dogs were

* The Dial-Urethane was generously supplied by the Ciba Pharmaceutical Co., Rahway, N. J.

permitted to recover. Those that died were autopsied immediately.

A series of 10 additional dogs were studied in a similar fashion to those described above, except that hemorrhagic hypotension was not produced. These animals served as triple controls to assess the effects of the manipulative procedures and the duration of anesthesia.

Results

A. *Metabolic*

1. *Oxygen* (*table 1*). The systemic arterial oxygen content decreased progressively during shock. This was the result of hemodilution plus some arterial oxygen unsaturation. Along with the low cardiac output, the pulmonary artery oxygen content decreased to very low levels. In a few dogs it was even lower than the coronary sinus oxygen after three hours of hypotension. The coronary sinus oxygen content was significantly decreased, however, and the coefficient of extraction of oxygen was significantly increased from the control value of 64 per cent, to 85 per cent after three hours of hypotension. With this increase in the per cent extraction of oxygen and the maintained rate of coronary flow, the total utilization of oxygen by the myocardium was maintained within normal limits.

2. *Carbohydrate* (*table 2 and figures 1 and 2*). The arterial level of pyruvate increased from the control value of 1.59 mg. per 100 cc. to 2.83 mg. per 100 cc. in the immediate post-hemorrhagic period and to 3.82 mg. per 100 cc. three hours later, a value approximately two and one-half times the initial blood level. The pyruvate arteriovenous difference was not significantly increased in the early period of hypotension, so that the pyruvate extraction coefficient was significantly decreased. After three hours of hypotension the changes were much more striking, with a negative coronary arteriovenous difference. As seen in figure 1, the values were shifted somewhat to the right of the normal regression line immediately after hypotension was established, reflecting the decreased coefficient of extraction. Three hours later, however, the values for pyruvate arteriovenous differences were either negligible or actually negative, despite the high arterial pyruvate levels.

The changes in lactate extraction were similar to those for pyruvate in the immediate period of hypotension (figure 2). There was a slight increase in the arteriovenous difference, which was not proportionally as great as the increase in arterial level, so that the extrac-

Table 1.—A. *Effects of Shock on Oxygen Metabolism* (*Mean* $\pm\sigma m$)

	O_2 Cont. vol. %			L.V.O_2 Util. ml/100 Gm./min.	C. Ext. O_2 %	Myoc. R.Q.	B.O.C. ml/M^2/ min.	Art. O_2 SAT. %	Art. CO_2 Cont. vol. %	Art. pH	Resp. Vol. L/min.
	Ao.	P.A.	C.S.								
Initial control period	17.8	13.5	6.3	15.4	63.6	.86	111.9	91.7	44.0	7.21	3.5
	±.6	±.6	±.7	±2.7	±3.8	±.03	±9.9	±1.6	±1.5	±.02	±.5
Immed. after hemorrh.	14.5*	5.6*	2.7*	11.2	81.4*	.91	107.1	87.8	32.4*	7.22	6.7†
	±.7	±.7	±.3	±1.7	±1.6	±.03	±9.1	±2.0	±1.9	±.01	±1.2
3 hours after hemorrh.	11.5*	2.0*	1.7*	13.3	84.6*	.95	89.7	81.0	21.4*	7.21	7.9*
	±.9	±.5	±.2	±5.9	±2.2	±.04	±7.6	±5.9	±2.5	±.03	±1.3
B. Triple Control Observations											
Initial control	17.3	13.9	6.5	11.9	62.4	.85	113.8	87.7	45.3	7.26	3.3
	±.7	±.6	±.6	±1.0	±3.5	±.03	±8.9	±2.4	±1.4	±.03	±.3
3 min. control	17.3	13.7	6.2	12.6	64.5	.88	122.4	88.6	42.9	7.25	3.6
	±.7	±.6	±.6	±.9	±3.5	±.04	±13.1	±2.5	±1.2	±.03	±.3
3 hour control	17.5	11.9	5.2	16.0	70.4	.87	151.0	92.0	41.1	7.26	4.3
	±.5	±.9	±.6	±6.2	±4.1	±.05	±21.6	±2.6	±1.8	±.02	±.6

* Significant change from initial control period, $p < .01$.

† Change from initial control period of borderline significance, $p < .05 > .01$.

Abbreviations: Ao. = aortic; Art. = arterial; B.O.C. = total body oxygen consumption; C.Ext. = myocardial coefficient of extraction (A-V/A); C.S. = coronary sinus; L.V. = left ventricle; P.A. = pulmonary artery; Resp. Vol. = respiratory volume; R.Q. = myocardial respiratory quotient; Sat. = saturation; σm = deviation of the mean.

TABLE 2.—A. *Effects of Shock on Carbohydrate Metabolism (Mean ±σm)*

	Pyruvate				Lactate				Glucose			
	Ao. mg. %	A-V mg. %	Util. mg/100 Gm./min.	C. Ext. %	Ao. mg. %	A-V mg. %	Util. mg/100 Gm./min	C. Ext. %	Ao. mg. %	A-V mg. %	Util. mg/100 Gm./min	C. Ext %
Initial control period	1.59 ±.15	.80 ±.11	1.20 ±.34	49.8 ±3.9	11.2 ±1.4	5.9 ±.9	7.2 ±1.1	53.5 ±4.9	90.2 ±3.4	4.7 ±.8	6.3 ±1.3	5.0 ±.9
Immed. after hemorrh.	2.83* ±.23	.96 ±.13	.82 ±.13	34.4† ±4.3	38.0* ±5.0	9.9† ±1.5	12.1† ±2.0	31.1* ±5.7	180.0* ±23.8	4.6 ±2.3	3.8 ±2.0	3.8 ±1.5
3 hours after hemorrh.	3.82* ±.42	−.37* ±.22	−.54* ±.45	−9.6* ±6.5	75.2* ±8.7	10.4† ±1.9	13.0† ±2.7	15.0* ±2.5	160.8 ±42.2	1.8 ±2.4	1.9 ±3.0	.4 ±1.9
B. Triple Control Observations												
Initial control	1.55 ±.22	.81 ±.15	.84 ±.15	49.9 ±4.3	11.4 ±1.9	5.9 ±1.3	6.1 ±1.3	49.0 ±3.3	82.1 ±5.0	3.2 ±.5	3.6 ±.8	4.1 ±.7
30 min. control	1.63 ±.23	.82 ±.14	.85 ±.12	49.3 ±2.6	13.1 ±2.2	6.6 ±1.2	7.0 ±1.1	50.6 ±2.9	82.0 ±7.9	4.7 ±1.2	5.0 ±1.4	6.4 ±1.2
3 hour control	1.58 ±.12	.66 ±.06	.82 ±.29	42.3 ±3.3	13.7 ±2.0	6.5 ±1.0	9.4 ±4.8	46.9 ±1.5	87.1 ±6.2	8.1 ±3.0	14.6 ±8.4	9.1 ±3.3

* See table 1.

† See table 1.

Abbreviations: See table 1; A-V = coronary arterio-venous difference.

tion coefficient was significantly reduced. After the dogs were hypotensive for three hours, however, the lactate findings were in marked contrast to those for pyruvate. The arterial lactate level at this time was almost seven times the control value. The arteriovenous difference and total utilization were still significantly positive, although the extraction coefficient decreased.

The arterial glucose level increased significantly during the immediate posthemorrhagic period, but after three hours there was a great deal of variation. In some animals the elevated levels were maintained or increased, whereas they dropped in other animals. The ability to maintain the elevated level of glucose could not be correlated with the eventual survival or death of the dog. There was also much variation in the findings for glucose extraction with no significant change from the control period, except for the consistently decreased glucose extraction coefficient after three hours.

B. *Hemodynamic (table 3)*

Since both arterial blood pressure and cardiac output were decreased during shock, left ventricular work was correspondingly lowered. There was much variation in the values for coronary flow, but despite the very low systemic arterial pressures and low cardiac outputs during shock, the coronary flow was not decreased. Myocardial oxygen utilization was thus maintained (see table 1) with consequent marked reduction in the mechanical efficiency of the heart during the hypotensive

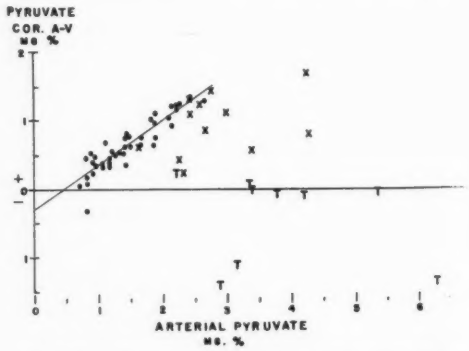

FIG. 1. Relation of coronary arteriovenous difference to arterial level of pyruvate. Open circles represent normal control values, x = values during intermediate posthemorrhagic period, and T = values after three hours of sustained hypotension.

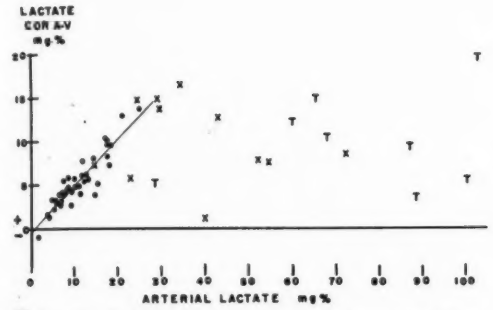

FIG. 2. Relation of coronary arteriovenous difference to arterial level of lactate. Open circles represent normal control values, x = values during immediate posthemorrhagic period, and T = values after three hours of sustained hypotension.

period. After three hours of hypotension the coronary vascular resistance was significantly decreased to less than half that of the initial control value, indicating coronary vasodilatation. At the same time there was marked variation in both systemic and pulmonary vascular resistance, so that no significant changes could be demonstrated during the experimental period. The heart rate increased strikingly from the control mean value of 76 to 174 after three hours of hypotension.

C. *Pathologic*

Out of nine dogs subjected to the full three-hour period of hemorrhagic shock, five died without regaining a normal stabilized blood pressure level despite reinfusion of all removed blood. When the hearts were excised there was marked subendocardial hemorrhage in the left ventricle of two of these dogs (fig. 3), and three showed marked hyperemia and submucosal hemorrhage in the small intestine (particularly in the duodenum). In one of the five dogs no pathological changes were found. Of the four dogs that survived the immediate postexperimental period, two survived until they were sacrificed seven months later. Two died within two weeks and in both foci of myocardial necrosis were present, especially in the subendocardial region of the left ventricle (fig. 4). No significant correlations could be made between the metabolic findings, and the survival or death of the animal, or the nature of the pathological findings.

D. *Triple Controls*

There were no significant changes in any of of the observations throughout the duration of the triple control period. There was much

TABLE 3.—A. *Hemodynamic Effects of Shock (Mean ±σm)*

	MAPB mm. Hg.		C.I. L/M²/min	Cor. Flow ml/100 Gm./min	C.F./C.O. %	L.V. work Kg./min	L.V. Eff. %	Heart Rate per min	Vasc. Res.		
	Ao.	P.A.							Syst.	Pulm.	Cor.
Initial control period	121.2	11.1	3.4	136.9	5.4	5.1	15.8	76.3	2.31	.275	58.2
	±4.5	±.7	±.5	±20.3	±.8	±1.0	±2.5	±3.1	±.31	±.037	±11.4
Immed. after hemorrh.	54.3*	5.6*	1.2*	94.7	11.0*	.8*	3.8*	147.5*	2.09	.372	45.1
	±2.3	±.6	±.1	±15.4	±1.7	±.1	±.9	±11.5	±.39	±.075	±8.5
3 hours after hemorrh.	45.6*	6.9†	1.0*	121.1	18.9*	.6*	2.2*	174.3*	1.68	.579	26.2*
	±3.5	±1.9	±.1	±20.0	±4.4	±.1	±.3	±18.0	±.34	±.251	±4.2
B. Triple Control Observations											
Initial control	123.2	11.4	3.6	114.4	4.2	5.3	20.1	81.9	2.10	.156	73.5
	±4.0	±.9	±.4	±11.4	±.4	±.7	±1.6	±10.8	±.25	±.029	±10.6
0 min. control	118.2	10.3	3.6	116.0	4.3	5.1	17.8	84.0	1.96	.117	65.7
	±3.8	±.6	±.3	±9.6	±.4	±.5	±.8	±8.7	±.17	±.015	±6.7
hour control	130.0	11.6	2.7	125.6	6.1	4.1	15.6	78.0	2.78	.304	85.9
	±4.4	±.3	±.2	±44.7	±2.0	±.5	±3.7	±9.0	±.22	±.022	±17.9

* See table 1.

† See table 1.

Abbreviations: See table 1; CF/CO = coronary flow ÷ cardiac output; C.I. = cardiac index; Cor. = coronary; Eff. = efficiency; MABP = mean arterial blood pressure; Pulm. = pulmonary; Syst. = systemic, Vasc. Res. = vascular resistance.

FIG. 3. Section of left ventricle of dog that did not recover from shock. Note massive subendocardial hemorrhage. Endocardial surface at top. Hematoxylin and eosin. 162 ×.

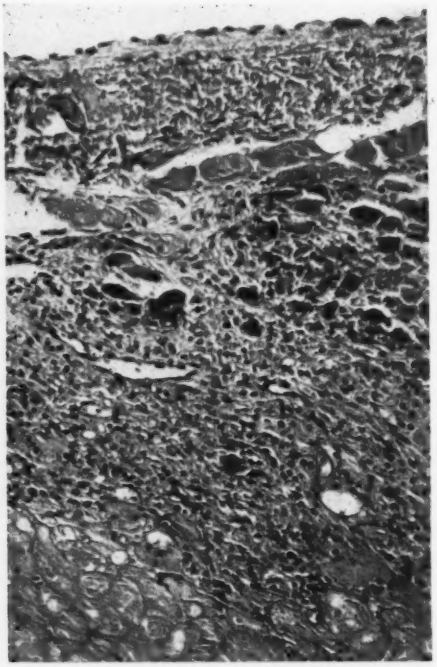

FIG. 4. Section of left ventricle of dog that died two weeks after initial recovery from shock. Note the necrosis and inflammatory infiltrate in the subendocardial region. Endocardial surface at top. Hemat oxylin and eosin. 162 ×.

random variation after three hours, however, particularly in the values for coronary flow, cardiac output and vascular resistance.

DISCUSSION

A negligible or negative myocardial pyruvate extraction was the most consistent and striking abnormality found during hemorrhagic shock of three hours duration. A possible mass action effect of the disproportionately elevated lactate level might be suspected in suppressing pyruvate extraction and utilization but for the following evidence to the contrary: In previous experiments we have shown that glucose, lactate and pyruvate extractions appear to depend primarily on the arterial level of each metabolite independent of other substrate concentrations.[7] In addition, lithium lactate infusions, to produce elevated lactate levels comparable to those in shock, were found recently to have no effect upon pyruvate extraction.[8]

Both glucose and lactate extractions were maintained by the myocardium during shock, although at greatly increased arterial levels, with correspondingly reduced myocardial extraction coefficients. The somewhat similarly altered pattern of myocardial carbohydrate extraction observed in thiamin deficiency may be due to a deficiency in co-carboxylase,[9] and in diabetic heart muscle, to insulin lack.[10] In starvation,[7] anoxia,[11] as well as in the presently described state of hemorrhagic shock, comparable reductions in myocardial carbohydrate extraction coefficients occur without known cause. In congestive heart failure due to valvular heart disease, however, the pattern of myocardial carbohydrate metabolism is quite different with normal or greatly elevated glucose extraction coefficients, and a well maintained extraction of lactate and pyruvate.[10]

A failure of myocardial energy productio

may be reasonably postulated in hemorrhagic shock, along with the other conditions mentioned above, as suggested by Olson and Schwartz.[12] This again contrasts with congestive heart failure where one suspects a failure of conversion of chemical energy into effective mechanical work as the primary defect. In both types of situation the heart is mechanically inefficient. Whether the extreme tachycardia is the result or, in part, the cause, of an altered pattern of energy production and defective conversion is not yet clear. The presence of tachycardia is almost certainly significant as a sign of stress, and is accompanied by a release of adrenalin and adrenocortical hormones in increased quantity to account for the extreme rise in circulating glucose, lactate and pyruvate. Yet tachycardia alone, observed in comparable degree in normal nembutalized dogs, was accompanied by a normal myocardial metabolic pattern and mechanical efficiency.[6, 7] Tachycardia plus maximal coronary vasodilation under the influence of local metabolic stimuli could account for the remarkable maintenance of coronary flow despite the presence of oligemic shock with greatly diminished systemic blood pressure and cardiac output. Again, the role of increased circulating epinephrine, a potent coronary vasodilator, is fairly certain. The pH remained normal and serum carbon dioxide was kept at a minimum through hyperventilation in these experiments, and thus probably contributed little, if any, to the coronary vasodilation.

Myocardial oxygen consumption was remarkably unchanged throughout the prolonged period of hemorrhagic shock, although some reduction relative to the greatly diminished cardiac work might have been expected. The mean myocardial oxygen extraction coefficient was actually increased, from 64 per cent to 85 per cent, indicating relative myocardial hypoxia and coronary insufficiency. The local tissue hypoxia could well be the initiating factor favoring maximal coronary vasodilation. Full compensation for myocardial hypoxia through optimal increases in coronary flow could have been thwarted by the low arterial coronary perfusion pressure and low cardiac output, thus forcing the myocardium to increase its oxygen extraction coefficient.

The maintenance of myocardial oxygen consumption despite acutely reduced cardiac work, with marked tachycardia and relative myocardial hypoxia in hemorrhagic shock, is in sharp contrast to the effects of the hypotension produced by spinal anesthesia.[13] Here there is no tachycardia, a reduced myocardial oxygen extraction coefficient, and a diminished coronary flow paralleling the fall in blood pressure. The basic difference between the two states is between hyper- and hypoactivity of the sympathetic nervous system. It is tempting to postulate that extreme sympathetic hyperactivity, as in hemorrhage, anoxia and other conditions involving acute stress, causes an alteration in myocardial metabolism of the pattern presented, with inefficiency in the performance of mechanical work. This may predispose to the terminal circulatory and cardiac failure that eventually occurs.

Summary

The metabolic, hemodynamic and pathologic effects of hemorrhagic shock on the hearts of intact dogs have been reported.

Metabolic studies demonstrated alterations in the pattern of myocardial carbohydrate metabolism during shock, the most striking change being a reduction in the normally high myocardial extraction coefficient of pyruvate to negative values.

Oxygen was extracted by the heart in relatively large amounts in comparison with the small amount of mechanical work done, resulting in very low values for myocardial efficiency. Nevertheless, a relative oxygen deficiency was indicated by the increased myocardial oxygen extraction coefficient.

Subendocardial hemorrhage or necrosis was found in the left ventricles of some of the dogs. No correlation could be found, however, between the nature of the pathological findings, the immediate survival of the animal or the metabolic alterations.

The changes observed can best be ascribed to hyperactivity of the sympathetic nervous system and increased circulating adrenalin

with a myocardial metabolic pattern similar to other situations involving severe shock.

Summario in Interlingua

Es reportate le effectos metabolic, hemodynamic, e pathologic de choc hemorrhagic super le cordes de canes intacte.

Studios metabolic demonstrava le occurrentia, durante le choc, de alterationes in le configuration del metabolismo myocardiac de hydratos de carbon. Le plus frappante de iste alterationes esseva le reduction, usque a valores negative, del normalmente alte coefficiente de extraction myocardiac de pyruvato.

Viste le parve quantitate de labor mechanic, le quantitate de oxygeno extrahite per le corde esseva relativemente grande. Le resultato esseva bassissime valores pro le efficacia myocardiac. Nonobstante, un deficientia relative de oxygeno esseva revelate per le augmentate coefficiente myocardiac de extraction oxygenic.

Hemorrhagia o necrosis subendocardiac esseva observate in le ventriculo sinistre de alicunes inter le canes. Sed nulle correlation esseva establibile inter le natura del constatationes pathologic, le superviventia immediate del animales, o le alterationes metabolic.

Il pare melio ascriber le alterationes observate a un hyperactivitate del systema nervose sympathic e a un augmento de adrenalina circulante. Il esseva permissibile concluder que le configuration del metabolismo myocardiac resimilava illo trovate in altere situationes de choches sever.

Acknowledgments

We would like to thank Dr. Thomas D. Kinney for his advice and encouragement. Acknowledgement is also given for the excellent technical assistance of Ernest Shiwanov, Eileen Mikat and Jacqueline Berg.

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Nomogram for Simple Calculation of Cardiac Output

By CHARLES EUGENE JACKSON, M.D.

A nomogram is presented which facilitates the determination of cardiac output from blood pressure measurements and the patient's age using the formula presented by other authors.

THE purpose of this paper is to present a nomogram which will facilitate calculation of cardiac output, utilizing blood pressure determinations and the formula developed by Isaac Starr and Truman G. Schnabel, Jr., in their work in simulated systole at necropsy. The formula suggested initially[1] was:

Stroke volume = 91 + 0.54 pulse pressure − 0.57 diastolic pressure − 0.61 age.

This formula related the stroke volume to femoral intra-arterial pressure measurements but in a later paper by these authors and others[2] another formula was presented relating the stroke volume to auscultatory blood pressure measurements with the diastolic level taken at the point of disappearance of the sounds. This formula was given as:

Stroke volume (cc) = 101 + 0.50 pulse pressure (mm Hg) − 0.59 diastolic pressure (mm Hg) − 0.61 age (years).

They suggested that by using this formula and multiple blood pressure determinations to

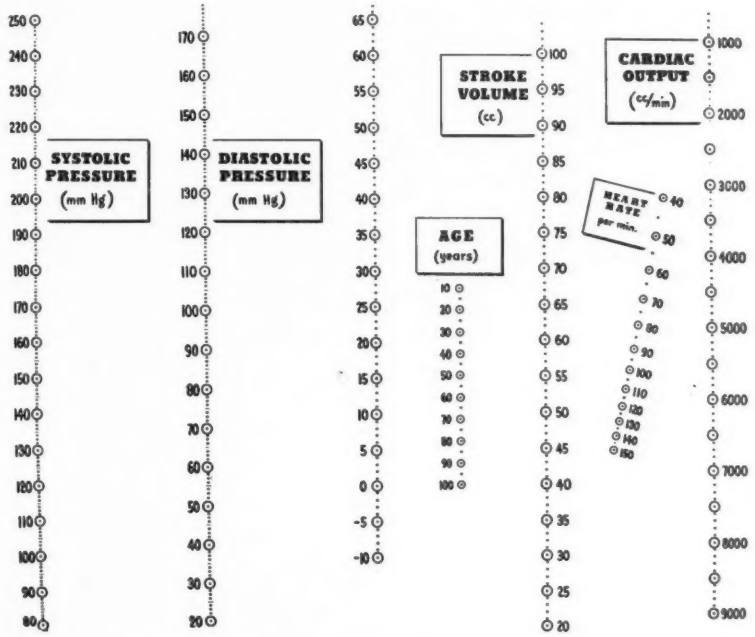

FIG. 1. With a straight edge match the systolic pressure with the diastolic pressure to obtain a figure on the center column which matched with the age indicates the stroke volume on the proper column. Stroke volume matched with the heart rate then indicates the cardiac output.

decrease the scatter due to random fluctuations, the error in two-thirds the estimates would diminish towards a value of less than 5.9 cc.

A comparison of this method with other more elaborate techniques for measuring cardiac output by the Fick, dye, acetylene, ethyl iodide and nitrous oxide methods showed a reasonable correlation in a variety of clinical and physiological conditions.[3] Though further comparative studies are indicated, this work suggests that a means is now available to make a rough estimation of cardiac output as a routine part of the examination of every patient so that the physician taking blood pressures can interpret the findings with greater insight into their physiological meaning.

The nomogram (fig. 1) presented will enable the physician using this formula to determine stroke volume and cardiac output more readily.

Addendum

Additional derivation of the formula necessary to construct the nomogram[4] is presented:

1. Stroke volume (cc) = 101 + 0.50 pulse pressure (mm Hg) − 0.59 diastolic pressure (mm Hg) − 0.61 age (years).[2]

Since pulse pressure = systolic pressure − diastolic pressure.

2. Stroke volume = 101 + 0.50 (systolic pressure − diastolic pressure) − 0.59 diastolic pressure − 0.61 age.

3. Stroke volume = 101 + 0.50 systolic pressure − 0.50 diastolic pressure − 0.59 diastolic pressure − 0.61 age.

4. Stroke volume (cc) = 101 + 0.50 systolic pressure (mm Hg) − 1.09 diastolic pressure − 0.61 age.

Summario in Interlingua

Es presentate un nomogramma pro determinar le rendimento cardiac super le base de mesurationes del pression sanguinee e le etate del patiente. Le nomogramma es disveloppate ex un formula previemente presentate per Isaac Staar e co-laboratores. Volumine per pulso = 101 − 0,50 del pression del pulso −0,59 del pression diastolic − 0,61 del etate.

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CLINICAL PROGRESS

EDITOR: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

The Clinical Results in the First Five Hundred Patients with Mitral Stenosis Undergoing Valvuloplasty

By LAURENCE B. ELLIS, M.D. AND DWIGHT E. HARKEN, M.D.

A report is made of the clinical results in the first 500 patients operated on by mitral valvuloplasty in whom a preoperative diagnosis of predominant mitral stenosis had been made. The operation appears to offer some protection against late peripheral embolization.

Four hundred forty of 442 surviving patients have been followed for periods of from six months to five years. Seventy seven per cent of the entire group are significantly improved. Thirty one per cent have had one or more attacks of a postoperative syndrome, but in only 7 per cent has there been clear-cut evidence of active rheumatic fever. Improvement in objective clinical findings, in particular in cardiac murmurs, heart size and the electrocardiogram, have been less striking than the subjective improvement.

SURGICAL treatment for mitral stenosis has now existed for sufficient time and has been carried out on enough patients to permit evaluation of operative mortality and postoperative results for the first few years. The earlier efforts of Cutler, Graham and others were largely directed at the conversion of mitral stenosis into mitral insufficiency. It was argued that incompetence was to be preferred to obstruction. Souttar attempted digital dilatation and no doubt attained a remarkable degree of restoration of valve function in one patient. His effort was not sustained nor his contribution appreciated. The reactivation of surgical efforts in the field stemmed from consistently successful intracardiac surgery during World War II and a better appreciation of the significance of individual leaflet function. We have described elsewhere[1-3] the development and details of the operation and the rationale for use of the term valvuloplasty, which we have given it. Smithy, a postwar pioneer in this field, unfortunately died before he could extend his initial experiences.[4, 5] Bailey with his collaborators[6-8] in this country has termed his operation commissurotomy, and Baker, Brock and Campbell[10, 11] in England refer to it as valvulotomy and valvotomy.

The place of any operation in the treatment of a pathologic state must be judged by the following standards: The course of the disease under medical management; the operative mortality; the benefit to be derived from operation. It is our purpose in this article to present evidence dealing with the second and third points and to show that there is a useful place for mitral valvuloplasty in properly selected patients.

This report deals with our first 500 patients in whom a preoperative diagnosis of predominant mitral stenosis was made. The operative technic has been described previ-

[This study was presented at the Second World Congress of Cardiology, Washington, D. C., September 14, 1954.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital; the Surgical Service of the Peter Bent Brigham Hospital, and the Departments of Medicine and Surgery, Harvard Medical School.

The study was supported by Grant #442 of the National Heart Institute.

ously by us[2] and probably changed only qualitatively rather than in principle in this group of 500 patients. With confidence and skill gained through experience, the surgeon has been able to accomplish increasingly successful valvuloplasty by the appropriate use of his finger or a valvulotome, depending on the condition of the valve. Since embolization to peripheral arteries has proved to be a major problem at the time of operation, techniques to minimize this danger were adopted in the last 250 patients in this series. The possibility of intra-auricular thrombi being present is greatest in fibrillating patients, and, therefore, in all of these the auricle has been freely flushed before any intra-auricular manipulation. Because cerebral emboli have proved the most disastrous, it was also hoped that isolation of the cerebral circulation at the time of the greatest danger of detachment of emboli, as suggested by Bailey and his co-workers,[11] might be of value. This was accomplished by tapes passed beneath the innominate, carotid, and left subclavian arteries by which angulation of the vessels cut off the cerebral blood flow for periods up to 60 seconds. This interruption of cerebral flow can be carried out repeatedly, with rest and recirculation between manipulation. This maneuver has not prevented embolization and the anoxia that it produces may have caused more harm than the theoretical benefit it confers. This technique has been largely abandoned except in patients with calcification of the mitral valve when it is employed at the time that the calcified area is cut or fractured. The many clinical details that may improve the quality of valvuloplasty and may reduce the danger of embolus from the auricle or calcification are considered in a separate discussion.[12]

TABLE 1.—*Operative Mortality of First 500 Patients Undergoing Valvuloplasty*

Patient Number	Group II and III		Group IV	
	No. of Patients	Mortality %	No. of Patients	Mortality %
1–100	59	14	41	32
101–200	74	3	26	27
201–300	76	7	24	21
301–400	72	4	28	21
401–500	74	2.7	26	27

SELECTION OF PATIENTS FOR OPERATION

Our criteria for the selection of patients for operation have not materially changed since early in our experience.[3] We believe now, as we always have, that patients should not be operated upon unless they are substantially disabled by their disease, and unless, in spite of medical treatment, they are going progressively downhill. The reasons for this attitude are obvious. Many persons may have a very benign form of mitral valve disease, and before the onset of symptoms it is usually difficult to foretell what the course of their illness will be; they may never need an operation. It must be remembered also that this operation, in its present form, is a palliative procedure, not a cure. The valve is not restored to normal, and other factors in the heart disease, not dependent on the mechanical obstruction, are not relieved. We are undoubtedly somewhat more liberal now than we were in accepting some patients with lesser degrees of disability, who find it difficult to accept their limitations for reasons of occupation or otherwise.

The classification, which has been employed, has been described elsewhere;[3] it roughly corresponds to the functional classification of the New York Heart Association. This series includes no patients in group I, that is those without any significant symptoms. It includes only 13 in group II; these are patients who are handicapped by symptoms from their disease but in whom the condition is not particularly progressive. There are 342 in group III; patients suffering mainly from pulmonary symptoms which are progressive in nature and sufficiently handicapping so that ordinary activities are being significantly and increasingly limited. There are 145 in group IV; these being cardiac invalids, mostly suffering from chronic congestive failure.

OPERATIVE MORTALITY

The operative mortality is shown in table 1. This includes not only patients who died at operation, but also those who failed to rally in

he postoperative period. The cases are divided nto consecutive hundreds of patients. Since here are so few cases in group II and only ne operative death, these are included with group III. It will be seen that in this category, after a relatively high mortality in the initial cases, the mortality experience has markedly improved so that it is under 3 per cent in the last hundred. Indeed, in the last 200 group III patients operated on since this series of 500 was complete, there has been only one death. On the other hand, the death rate in the group IV patients has remained in the neighborhood of 25 per cent. This emphasizes the desirability of operating upon mitral disease patients before they reach this terminal stage, at which time the operative mortality is high and less dramatic results from the operation will usually be achieved.

The apparent lack of improvement in the operative mortality in group IV patients may be due to a number of factors and will be considered in a subsequent report. Suffice it to say that the dramatic improvement in technique, that is reflected in the reduction of mortality in group III patients to something that may now approximate 1 per cent, has probably been balanced in the group IV patients by better preoperative medical care that brings to operation patients who formerly succumbed before surgery. Furthermore, many of the patients now obtaining successful surgery formerly were not even considered for operative intervention. Thus better surgical technique and vastly improved postoperative regimen are certainly masked by a shift of preterminal patients into the operative experience.

When the effect of age on the operative mortality is considered (table 2), it will be seen that there is no clear trend toward increasing risk with advancing age, provided the distinction between group III and IV patients is maintained. Proportionately, a progressively larger number of patients fall into the group IV category as age advances.

Table 3 shows the effect of auricular fibrillation in increasing operative mortality. This is clear in the group II and III patients in the last 400 patients. Six patients in group III who were in normal sinus rhythm died in the first group of 100 patients as a result of technical problems related to operation, unsolved at that time. In group IV there were too few patients in normal sinus rhythm to be of statistical significance, but there was only one death in patients in normal rhythm as compared with a mortality of 31 per cent in the fibrillating patients. The relation of the operation to the precipitation of peripheral emboli will be discussed later.

Follow-up Results

There were 442 patients who survived the operation and of these all but two have been followed for a period of at least six months (table 4). Four hundred and nine have been followed from one to five years. The mean follow-up time for the entire group is 22 months.

Evaluation of the postoperative status of the patients has been based on all available information, including questionnaires to pa-

Table 2.—*Effect of Age of Patient on Operative Mortality*

Age in Years	Group	Number of Patients	Number of Operative Deaths	Operative Mortality %
10–19	II & III	3	0	0
	IV	0	0	—
20–29	II & III	67	4	6
	IV	6	2	33
30–39	II & III	148	8	5
	IV	35	8	23
40–49	II & III	122	8	6
	IV	66	13	20
50–59	II & III	14	0	0
	IV	35	15	43
60–69	II & III	0	0	—
	IV	3	0	0

Table 3.—*Effect of Auricular Fibrillation on Operative Mortality*

Group	Rhythm	Cases 1–100			Cases 101–500		
		No.	No. Dead	% Dead	No.	No. Dead	% Dead
II & III	AF	23	2	9	126	7	6
	NSR	36	6	17	170	5	3
IV	AF	34	12	35	86	25	29
	NSR	7	1	14	18	0	0

TABLE 4.—*Duration of Follow-up of the First 500 Patients Undergoing Mitral Valvuloplasty*

6 months–1 year	31
1–2 years	230
2–3 years	127
3–4 years	42
4–5 years	10
Total followed	440
Lost	2
Operative deaths	58
Total	500

Mean follow-up time, 22 months

TABLE 5.—*Follow-up Results in the First 442 Patients Surviving Mitral Valvuloplasty*

	Group II		Group III		Group IV		Total Patients %
	No.	%	No.	%	No.	%	
Improved markedly	7	58	181	56	54	51	77
moderately	3	25	80	25	15	14	
slightly	0	—	25	8	12	11	
Unchanged	2	17	20	6	12	11	
Worse	0	—	8	2.5	3	3	23
Late Deaths	0	—	8	2.5	10	9	
Lost	0	—	1	—	1	1	
Total	12		323		107		

tients, reports from their physicians, and personal examinations in as many as possible. All of the surviving patients were sent questionnaires in September 1953 and again in July of 1954. These questionnaires were designed to test not only the patients' subjective feelings but to get as much information as possible regarding any change of activities, change of treatment, and so forth, in order that an objective estimate could be gained. In addition, reports from the patients' physicians and personal examinations were obtained on as many as possible. Further consideration of this will be given later.

The results in each group are shown (table 5). In the group II patients all but two are clearly improved. In group III, eight have died, one of a noncardiac cause, and 28 are unchanged or worse than before operation. Five of these latter patients are disabled by the residua of operative emboli to such an extent that they have not been classed as better although in most of them the cardiac reserve has improved. The remaining patients in group III have improved, the vast majority markedly, which means that such patients are living essentially normal lives.

The results in group IV have also been strikingly good (table 5). Ten have died, one of whom succumbed to a noncardiac illness. Fifteen are unchanged or worse. Two of these are disabled as the result of operative or postoperative emboli although their cardiac status is better. The other patients in group IV are better, and more than half of the entire group have been strikingly improved. Since patients in this group were cardiac invalids, we have been somewhat more liberal in our definition of "marked improvement" and have so classified patients who can now carry on sedentary occupations and who require only a minimum of diuretic therapy.

Operative and Postoperative Embolization

Of particular interest is the effect of the operation on the precipitation of peripheral emboli and on the incidence of emboli developing at some late date after the operation.

Operative emboli detached from the thrombus in the left auricular appendage at the time of operation or from a calcific fragment of a fractured mitral valve constitute a major hazard of the procedure both in regards to mortality and in producing serious sequelae, usually in the form of cerebral hemiplegia, which may be disabling. Table 6 shows the incidence of these operative emboli in patients with and without auricular fibrillation. It will be seen from the table that the incidence of peripheral embolization is considerably higher in the patients who were fibrillating than in nonfibrillators, and in patients of group IV as compared with those of group III. It is of interest that of those patients in normal sinus rhythm who developed operative emboli, all but two had definitely calcified valves, and in these two, information was not clear as to whether or not calcification was present.

Of particular interest is the effect of the operation on the incidence of late peripheral

mboli. The danger of such emboli in patients with mitral stenosis, particularly in those in auricular fibrillation, is very real and is often one of the chief reasons for considering mitral valvuloplasty. Seventy-nine of the patients in this series of 500 had had one or more peripheral embolic episodes at some time prior to operation. All but eight were in auricular fibrillation at the time of operation, and some of these eight had had paroxysmal fibrillation in the past. None of these eight developed emboli at the time of operation, but 17 of the 71 in auricular fibrillation did. This is an incidence of 25 per cent in this relatively small group; emboli being more frequent in the group IV patients (33 per cent) than in group III (19 per cent). If these patients surmounted the hurdle of the operation, however, the chances of developing a late operative embolus are small. In the entire group of 440 surviving patients who have been followed for an average period of 22 months, or the equivalent of more than 800 patient years, there have been only five patients who have developed such peripheral emboli although more than half were fibrillating. It is our belief that this operation decreases the possibility of late embolization substantially.

We might interject here that subsequent studies may be expected to show that the techniques of avoiding operative emboli are improving.

Does the Stenosis Recur?

A crucial question is: Do the fractured valves again seal together and does the stenosis recur? We cannot give the answer as to the permanence of this operative relief, particularly since so little is known regarding the basic factors which lead to tight mitral stenosis and which usually develops insidiously many years after the first occurrence of overt rheumatic fever. However, this study supplies evidence concerning the results in the first five years postoperatively.

The most impressive evidence that the operation confers a genuine and lasting benefit is that in the overwhelming majority of instances, the improvement shown by the patients has been for the entire period of observation. Only one patient in group II, 18 in group III and 12 in group IV, a total of 31, have regressed substantially after a definite improvement persisting six months or more. These are now being studied in detail by us. In fifteen of these there were factors present which might explain the regression. These factors are: associated aortic valvular disease, poor operative fracture or leaflets that could not be mobilized, significant mitral insufficiency found to be present at the time of operation, or rheumatic fever occurring at some time since operation. About five we have as yet inadequate information. There are 11 regressions after an initial improvement for which there is not apparent a possible explanation. One cannot deny the possibility of refusion of the valve cusps in this small group, but the persistent good results in most of our patients suggest that this is most uncommon. Many of the so called refusions of valve cusps undoubtedly represent operations in which initially only dilatations were effected by the surgeon's exploring finger and in which the valves resumed their former size after a few weeks or months of this dilatation. In some of our own earlier cases, when the surgeon still lacked technical experience, only a dilatation or an inadequate fracture was effected. Five of these patients

TABLE 6.—*Incidence of Operative Peripheral Embolization in Fibrillating and Nonfibrillating Patients*

Case No. of Patients	Rhythm	Group III			Group IV		
		No. of Patients	No. with Emboli	%	No. of Patients	No. with Emboli	%
1–100	AF	23	3 (1)*	13	34	9 (6)*	26
	NSR	36	2 (1)	6	7	1 (0)	14
101–200	AF	29	1 (0)	3	22	4 (4)	18
	NSR	45	4 (0)	11	4	1 (0)	25
201–300	AF	34	2 (2)	6	20	2 (1)	10
	NSR	42	1 (1)	2	4	0 (0)	—
301–400	AF	30	5 (0)	17	24	3 (2)	12
	NSR	42	0 (0)	—	4	0 (0)	—
401–500	AF	33	1 (0)	—	20	2 (1)	10
	NSR	41	0 (0)	—	6	1 (0)	17
Total	AF	149	12 (3)	8	120	20 (14)	17
	NSR	206	7 (2)	3	25	3 (0)	12

* Numbers in parentheses denote number of fatal emboli.

have been reoperated upon for mitral stenosis. In every instance a note was made at the original operation that only dilatation or inadequate fracture was accomplished. These patients improved substantially for a period of six months to a year and then regressed more or less to their former condition. At the second operation, a more effective valvuloplasty was accomplished and the patients are again improved.

These unsatisfactory "dilatations" may well explain some of the 11 otherwise unexplained regressions. They are further examples of the fact that valvuloplasty can be qualitative. This quality should continue to improve.

Postoperative Syndrome

Others have noted the frequent occurrence postoperatively of a complex of symptoms first described by Soloff and his associates[13] and believed by them to represent reactivation of rheumatic fever. We have called it the "postoperative syndrome" since we are not convinced that it is always rheumatic fever. Indeed, it probably represents a mélange of conditions. The most striking manifestations of this syndrome are chest pain and fever. The chest pain may be of various types. It may be a deep, boring pain over the precordial area or pain which is difficult to distinguish from the intercostal pain common following thoracotomies; sometimes the pain is of the pleural type and may occur on either side; it may be noticed in the left shoulder.

Together with pain and fever, the syndrome may be characterized by pneumonitis on one or both sides, or by pleurisy either dry or with effusion. We have not included in this group postoperative manifestations within two or three weeks of operation, unless they are very clearly rheumatic fever, because of the difficulty of distinguishing them from the pericardial reaction which is inevitable after operation in these patients, and the pleural reaction secondary to the operation. Many patients also have shown a tendency to develop congestive symptoms following operation for a few weeks or even months. Inasmuch as there has been a profound change in the status of the hearts of persons successfully operated upon for mitral stenosis, it is usually unnecessary to attribute this to active carditis. It is obvious that the left ventricle has been protected by the severe degree of mitral stenosis in these patients, and when an effective fracture of the mitral valve has been made, this ventricle is called upon to do a great deal more work. It would not be surprising, therefore, if some degree of left ventricular failure occurred postoperatively, and it may take months before the left ventricle hypertrophies enough to accommodate itself to the increased work load it is called upon to carry. This would appear to be a physiologic adjustment to the change in the hemodynamics.

The majority of these patients with the postoperative syndrome were not personally observed in the attacks, which occurred after they had left the hospital, and we are dependent on information from them and their attending physicians. In some instances, no doubt, they reported attacks of incidental pneumonitis, bronchitis, exacerbation of the intercostal pain of the operative incision, and so forth, so that our reported percentage is undoubtedly a maximum. A further complicating factor has been a troublesome intercostal neuritis that occurred not infrequently in our earlier experience when Effocaine was used in the hope of preventing the postoperative intercostal pain. We found, as has been found elsewhere, that a neuritis resulted in a good many of these patients. This has been presumed to be due to the agent mentioned.

Thirty-one per cent of our patients have had one or more attacks of the postoperative syndrome following their discharge from the hospital after operation. Eighteen per cent had a single attack; in 13 per cent the attacks were recurrent. In some cases these attacks have recurred up to four years after operation. In 30, or 7 per cent, there was fairly good clinical evidence of rheumatic fever or arthritis. Further study is needed to elucidate the exact nature of these attacks and their relationship to the operative procedure. They have not proved to be sufficiently disabling in themselves, nor to have altered the improved status of our patients to a degree that would signif-

antly affect the overall operative benefit. Most of these patients have been treated with penicillin or other antibiotics at the time of these attacks and some have been given aspirin. Whether either of these types of treatment has altered the course, we do not know, since for the most part the attacks have been benign and have subsided within a week or two. All of our patients who are not sensitive to penicillin have been on prophylactic penicillin following operation. There has been no correlation between the presence of Aschoff bodies found in the biopsy of the auricular appendage of patients and the development of these attacks, and no evident correlation with their age and the severity or type of their symptoms prior to operation.

Objective Clinical Findings

A study is now in progress of the results of a follow-up examination on as many of these patients as possible, the examination being made personally by one of us or our associates. The results will be reported in detail elsewhere. A preliminary report on 67 of these patients is included here chiefly to show that the evaluation of their present status, based on our personal examinations, agrees closely with the evaluation made independently on the basis of questionnaires and similar information (table 7). On the whole, the personal examination revealed somewhat more favorable status than the questionnaires, but in no instance was there a marked discrepancy nor change of more than a single grade in the scale of improvement; for example, from "slightly improved" to "moderately improved" or from "slightly improved" to "unchanged." This close correlation between these two methods of evaluation in a significant sample of the whole group is evidence in favor of the validity of the evaluation of the entire series of 500 patients. Table 8 shows the present status of these patients classified according to the classification of the New York Heart Association with their status by this classification prior to operation.

Only a general statement will be made at this time regarding the objective findings in these patients. For the most part there has been neither dramatic nor consistent change in heart murmurs. Frequently the diastolic murmur has decreased and rarely has disappeared. In some instances an apical systolic murmur has appeared or has increased and occasionally it has decreased. There has also been no consistent changes in heart size. In a few instances it has become smaller and the pulmonary artery and its branches usually are smaller. The electrocardiogram for the most part has shown no change. Hence it can be said that the objective changes following mitral valvuloplasty are usually not striking.

Table 7.—*Evaluation of Follow-up Status of Patients Personally Examined*

	Questionnaires	Examination
Improved		
markedly	41	38
moderately	9	14
slightly	12	11
Unchanged	5	4
Total	67	67

Table 8.—*Preoperative and Postoperative Status of 67 Patients According to Classification of New York Heart Association*

Preoperative Classification	Number of Persons	Postoperative Classification			
		I	II	III	IV
II	1	0	1	0	0
III	49	20	20	9	0
IV	17	2	7	8	0
Total	67	22	28	17	0

Discussion

The literature is now replete with articles published on various phases of the operative relief of mitral stenosis. Those that are pertinent to this discussion and which bear on the clinical results following the operation are for the most part in agreement with the general conclusions reached in the present study.[8, 10, 14-27] Most of such published studies, however, deal with relatively few patients and with patients followed for only a short period of time. As we have emphasized previously, and has been noted by others both on clinical

grounds and as a result of hemodynamic studies, the improvement of these patients is often progressive over many months. This is undoubtedly due to the fact that the pulmonary vascular changes have regressed slowly over a period of months and that adjustments of the heart itself may also take place slowly. In the more seriously disabled patients, regression of changes in liver function as a result of the lessened congestion of the liver may also take place slowly.

Soloff and his associates[28, 29] have pointed out some of the problems in the evaluation of patients postoperatively and have indicated that the objective signs of cardiac improvement, particularly as to heart size, have lagged far behind subjective improvement. For this reason, and also because, in their experience, even the subjective improvement has not been too striking, they have questioned the advisability of operations for mitral stenosis in many patients with mitral valve disease.

It is difficult to get statistics on comparable groups of patients treated surgically and nonsurgically. This is particularly true in our group III patients who, as stated, are substantially disabled and going downhill. In view of the downhill course of these patients, it would seem likely that their outlook for continued life is not good; however, we have no statistics on patients of this type. The group IV patients are terminal cases, cardiac invalids. We previously reported[3] a series of 19 such patients who were acceptable for operation, but who refused it. Seventeen of the 19 were dead within one year.

It is true that the changes in physical findings are much less striking in our experience than the subjective improvement or the increased work capacity of these patients, and this holds true also in regard to some of the reported physiologic studies of circulatory function by cardiac catheterization. However, at the Second World Congress of Cardiology, a number of papers were presented showing a very favorable effect on cardiovascular physiology, particularly when measured several months after operation, and confirming a good many prior published reports of similar nature. It must be remembered that this operation is not curative; it is merely a palliative procedure, but often a very effective palliative procedure. It does not prevent the recurrence of rheumatic fever; in fact there is some evidence that rheumatic fever may occur more commonly following it than in patients unoperated upon. It does not prevent bacterial endocarditis, and where there is chiefly myocardial failure and valvular obstruction is not the important factor, it will not return such patients to health.

It is of course impossible to attribute the subjective improvement always to the mechanical effect of improved valve function produced by this operation. One cannot rule out other factors, such as the psychic effects of the procedure, and the fact that in some instances these patients have had more careful medical regulation subsequent to operation. However, patients with significant elements of symptomatology due to anxiety neurosis were excluded from the operation so far as possible, and most of the patients returned to the care of their own physicians after the operation, and on the whole have received less rather than more medical supervision. Other considerations also bear on this point. Thus, the improvement of these patients has for the most part been progressive over the first postoperative year and in almost all instances has been maintained during the period of observation. If the effects of the operation were largely psychic, one would expect the improvement to be immediate but less persistent. In addition, we are now in the process of analyzing in more detail a number of factors that affect the late results, and these, which will be reported elsewhere, show that good or poor results are in the aggregate dependent on factors having to do with the mitral stenosis per se, the severity of preoperative stenosis, the degree of calcification, the success in producing an adequately enlarged orifice, the amount of associated mitral insufficiency and other similar influences.

The 442 patients of the series surviving operation have had a death rate of 2.2 per cent per year, with death rates in groups III and IV of 1.5 per cent and 5.1 per cent, re-

spectively. The operative risk in group II and III patients is low, less than 3 per cent and may now approximate 1 per cent. The risk in group IV patients is still high, but is acceptable in view of the gravity of their sickness. When the fact is added that a high proportion of those suffering have had the downhill course of their disease reversed and have been restored to comfortable and useful lives, the evidence is conclusive that mitral valvuloplasty confers a genuine benefit on properly selected patients with handicapping symptoms.

Summary

A report is made of the clinical results in the first 500 patients operated by mitral valvuloplasty in whom a preoperative diagnosis of predominant mitral stenosis had been made. The progressive improvement in operative mortality in group III patients has been discussed. It is now less than 3 per cent and may approach 1 per cent. Certain factors affecting mortality have been considered, as well as the relation of operation to preoperative and postoperative embolization. The operation appears to protect against late peripheral embolization.

Four hundred forty of 442 surviving patients have been followed for periods of from six months to five years. The results in the various groups are described. Of the entire group, 77 per cent are significantly improved, and the improvement has been persistent in all but a small number; 31 per cent have had one or more attacks of a postoperative syndrome, characterized particularly by chest pain and fever, but in only 7 per cent has there been clear-cut evidence of active rheumatic fever. Improvement in objective clinical findings, in particular in cardiac murmurs, heart size and the electrocardiogram, have been less striking than the subjective improvement.

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ABSTRACTS

CONGENITAL ANOMALIES

Gross-Brockhoff, F., Schaede, A. and Lotzkes H.: Two Rare Cases of Transposition of the Great Vessels. Ztschr. f. Kreislaufforsch. **43**: 376 (June), 1954.

The authors report clinical, electrocardiographic, roentgenologic and angiocardiographic findings on two patients, 12 and 4 years old, both with congenital heart disease and severe cyanosis. The diagnosis of transposition of the great vessels suspected clinically was confirmed in both at autopsy. In the first case, both aorta and pulmonary artery originated in the right ventricle. There were two minor defects in the middle portion of the ventricular septum, but neither of the two vessels showed a true overriding. The outflow tract of the left ventricle was entirely absent. The second case revealed a "mirror image" of a Taussig-Bing syndrome with the pulmonary artery originating entirely from the left ventricle, and the aorta overriding a large high ventricular septal defect.

PICK

Adams, F. H., Lund, G. W. and Disenhouse, R. B.: Observations on the Physique and Growth of Children with Congenital Heart Disease. J. Ped. **44**: 674 (June), 1954.

In 229 children with congenital heart disease growth was studied using the well recognized Wetzel grid technique. The congenital lesions included those of patent ductus arteriosus, tetralogy of Fallot, interatrial septal defect, interventricular septal defect, coarctation of the aorta, and pulmonary stenosis without cyanosis. Statistical data show that individuals with these lesions exhibit normal growth patterns as measured by the Wetzel grid. It is the authors opinion for which no data is given that the abnormal growth pattern exhibited by some individuals with congenital heart lesions is from repeated respiratory infections promoted by pulmonary congestion incidental to the left to right shunt and in others genetic and emotional factors play a role rather than the heart lesion per se.

HARVEY

Wood, P.: An Appreciation of Mitral Stenosis. II. Brit. M. J. **1**: 1113 (May 15), 1954.

P mitrale when well-marked strongly favors stenosis rather than regurgitation. It should be present in all cases of stenosis severe enough to warrant valvulotomy. In three of the author's surgical cases it was not present, being replaced by P pulmonale (due to extreme pulmonary hypertension in two and to tricuspid stenosis in one). Judged by the six unipolar precordial leads, right ventricular preponderance correlated well with the presence and grade of increased pulmonary vascular resistance. Left ventricular preponderance was very rare in pure mitral stenosis but present in 82 per cent of the mitral regurgitation group.

By x-ray two-thirds of the surgical cases of mitral stenosis had an inconspicuous aortic knob. Radiological evidence of left ventricular enlargement was unreliable. The degree of dilatation of the pulmonary artery correlated well with pulmonary vascular resistance. In the group of pure mitral regurgitation the pulmonary artery was usually normal or only slightly dilated. The average of arbitrary figures for degree of left atrial enlargement was 1.62 for the surgical cases of mitral stenosis and 2.35 for cases of mitral regurgitation. Definite pulmonary hemosiderosis was present in 10% of the surgical cases of mitral stenosis and none of those of pure mitral regurgitation. Hemosiderosis may persist unchanged for a great many years. Pulmonary apoplexy had occurred in 55 per cent of the hemosiderotic group,

an incidence four to five times that in the non-siderotic group. *Heavy* mitral valve calcification was a reliable index of the presence of considerable mitral regurgitation.

By cardiac catheterization a *V* wave in the pulmonary venous pulse over 15 mm. Hg in amplitude almost always meant mitral regurgitation whereas a *V* wave under 5 mm. Hg in amplitude nearly always excluded it. In mitral stenosis the occurrence of congestive heart failure was intimately correlated with the development of very high pulmonary vascular resistance. For reasons not apparent congestive heart failure occurred in a case of mitral regurgitation with relatively little elevation of resistance. Only 20 per cent of cases of very high resistance gave a history of pulmonary congestive symptoms; no case of irreversible pulmonary hypertension was encountered; there was no correlation of the grade of elevation of resistance with probable duration of the pulmonary venous hypertension. These observations suggest that the high resistance is not exclusively the result of anatomical alterations in the pulmonary vascular bed. The author believes that pulmonary vasoconstriction is the physiologic response to mitral stenosis which is most important clinically because it determines the clinical pattern and course of the disease. The degree of stenosis as revealed at operation was the fundamental factor which determines the severity of the disease (angina pectoris, degree of pulmonary congestion, reduction in cardiac output). Atrial fibrillation and embolism were in the nature of accidents.

Post-operative atrial fibrillation occurred in 24 per cent of cases. Patients were routinely given digitalis for control of the ventricular rate should atrial fibrillation develop. Reversion was most easily accomplished toward the end of the second week. Anticoagulants were begun about the seventh day to prevent the formation of fresh clots —the type likely to embolize at the time of reversion.

The author's summary is a 2½ page synthesis of the clinical picture in each of the varieties of mitral valve disease. Although exception might be taken to occasional isolated and relatively minor points, this summary can be appropriately considered a classical description unexcelled in the existing medical literature.

McKusick

Grosse-Brockhoff, F. and Tseken G.: The Problem of Indication to Surgery in Mitral Stenosis. I. Pathologic-Anatomical Baseline. Ztschr. f. Kreislaufforsch. **43:** 403 (June), 1954.

On the basis of 85 autopsies of patients with mitral valvular disease, the frequency of indication to mitral surgery was investigated. One principal criterion is the presence of a pure, or functionally predominant, stenosis of the mitral ostrium, which can be diagnosed in the presence of a normally sized or atrophic left ventricle. This was found in 26 out of 50 cases of mitral disease without associated aortic lesions. Pure mitral insufficiency, on the other hand, was encountered in the material only four times.

The various combinations of mitral disease with other valvular lesions were analyzed with respect to operability. One-fourth to one-third of the mitral lesions can be expected to be associated with aortic involvement. In 17 cases, the tricuspid valve was affected in one case by severe stenosis. In no instance was an endocarditic lesion of the pulmonary valves encountered. One-fifth of the cases had adhesive pericarditis. In about half, the pulmonary vessels revealed microscopic sclerotic alterations. Hypertrophy and dilatation of the right ventricle present in all cases was especially marked in the presence of pulmonary sclerosis. Intracardiac thrombi were present in the left atrium in about half of the cases, in the right atrium in about 3 cases, and on occasion in the right or left ventricle. Calcification was observed in the mitral valve in 10 and in the aortic in 9 cases.

The time of observation from the rheumatic infection to death was one year to sixty years. The average duration of morbidity was 17.8 years for males and 14.8 years for females. In retrospect, mitral surgery would have been indicated in only one-fifth of the studied material. This estimate, however, may not reflect correctly the frequency of indications to commissurotomy during life since, obviously, the material was selected and represented cases with a poor outlook.

Pick

Kreutzer, R., Berri, J., Caprile, J. A. and Becu, L.: Patent Ductus Arteriosus in Infancy. Rev. argent. cardiol. **21:** 1 (Jan., Feb.), 1954.

Five cases of patent ductus arteriosus and left ventricular failure in infants less than five months old are reported. Four died due to left ventricular failure while one was successfully operated on. Three cases also had bilateral cataracts. In each instance, the mother had suffered from German measles during the first part of her pregnancy. The authors emphasize the importance of a correct diagnosis of this "malignant" type of ductus, because early ligation of the ductus is a life-saving procedure.

Luisada

Dimond, G. E. and Lin, T. K.: The Clinical Picture of Pulmonary Stenosis (Without Ventricular Septal Defect). Ann. Int. Med. **40:** 1108 (June), 1954.

The diagnosis of pulmonary stenosis should be suspected in patients with a harsh systolic murmur, maximal along the second, third, or even infrequently the fourth interspace, with a pulmonary second sound which may vary from normal to reduplicated or diminished and with an electrocardiogram which may vary from normal to one indicating right ventricular hypertrophy or right bundle branch block. Although the diagnosis can usually be made

after auscultation, electrocardiography, and fluoroscopy. Cardiac catheterization is the only reliable method for determining the presence of pulmonary stenosis in the intact patient and for differentiating the valvular from the infundibular types of pulmonary stenosis. Pulmonary stenosis is impossible to recognize consistently by angiocardiogram. Although pure pulmonary stenosis is generally a form of acyanotic heart disease, some decrease in peripheral arterial oxygen saturation is not uncommon. This is frequently due to a right-to-left shunt from the right to left auricle through either a patent foramen ovale or an auricular septal defect. Classically, the lung fields are said to be clear and ischemic. This is probably true in severe stenosis. However, the lung markings would be hard to differentiate from normal. There is considerable value in noting that the mid-lung pulmonary arteries never dance although the main pulmonary segment may be very prominent and active. This discrepancy in activity between the post-stenotic dilatation of the main pulmonary artery and its branches is clinically true and useful. The main pulmonary segment may be very large and active in valvular pulmonary stenosis. If the obstruction is in the ventricle (infundibular), the main pulmonary segment usually appears normal. Occasionally the right ventricle is so much enlarged that the post-stenotic dilatation is obscured by the protruding ventricle.

WENDKOS

Traisman, A. S. and Traisman, H. S.: Transient Complete Atrioventricular Heart Block of Unknown Etiology. Pediatrics **13:** 326 (Apr.), 1954.

A report of complete atrioventricular block in a boy nine years old is presented. Adams-Stokes syndrome occurred with the block. No cause for the abnormality was discovered and in three days the conduction defect changed to sinus rhythm with first degree heart block, and a right bundle branch block. Symptomatic treatment including atropine, ephedrine, and adrenaline was employed. The pediatric literature on the subject is reviewed.

HARVEY

Lyon, R. A. and Kaplan, S.: Patent Ductus Arteriosus in Infancy. Pediatrics **13:** 357 (Apr.), 1954.

Five cases of patent ductus in infants under two years of age are presented. The patent ductus in infancy can be a cause of severe cardiac failure, may cause repeated pulmonary infections and retardation of growth, or it can cause death. The diagnosis of a patent ductus is difficult for the tell tale murmurs do not become typical until the age of two or three. A persistent systolic murmur, slightly elevated systolic pressure, and slightly lowered diastolic pressure, prominent pulmonary artery and left ventricular hypertrophy on the roentgenogram suggest the diagnosis. Ligation was successfully performed on four of the infants under two years with prompt beneficial effects. The fifth infant died before operation could be done from infarction of one kidney secondary to thrombus in the renal artery and periarteritis and thrombus in the ductus.

HARVEY

Logan, A. and Turner, R.: Aortic Stenosis, Diagnosis and Treatment. Lancet **1:** 1091 (May 29), 1924.

In this general survey the authors note that dilatation of the ascending aorta is a common feature of these cases. Aortic valvulotomy was performed in nine severely disabled patients. Eight survived and were improved. Aortic and mitral stenosis when coexistent were corrected at the same thoracotomy in that order. The authors suggest surgery before the development of serious symptoms.

MCKUSICK

CORONARY ARTERY DISEASE

Keiser, C.: Statistical Studies Upon the Influence of Smoking Upon Angina Pectoris. Cardiologia **24:** 285 (Fasc. 5), 1954.

In 170 patients with established angina and myocardial infarction, and an equal number of controls of the same age group without any evidence of cardiovascular disease, a detailed history concerning smoking habits was obtained. A statistical analysis of the data revealed that the incidence of smoking was considerably greater in the abnormal than in the control group. Conversely in smokers, the incidence of angina pectoris or myocardial infarction was at least twice that of non-smokers, and was the greater the heavier the smoking. In the majority of the smokers, smoking per se was suggested to be the sole cause of coronary disease, while in about 75 per cent of non-smokers other possible etiologic factors could be established. These results are discussed in the light of some previous investigations concerning the influence of smoking upon intestinal absorption of fat and elevation of the chylomicron count in the blood serum.

PICK

Reiff, W. H.: Rupture of the Interventricular Septum Due to Myocardial Infarction: Report of Two Cases. Ann. Int. Med. **40:** 1125 (June), 1954.

Septal myocardial infarction with rupture of the interventricular septum due to myocardial infarction is discussed from the standpoint of electrocardiography and clinical observations. Two cases of septal perforation due to septal infarction are presented. Both were diagnosed antemortem, both were rapidly fatal, and the diagnoses were confirmed by autopsy. Diagnosis seems to be fairly obvious in most of the cases and depends upon the sudden appearance of a loud systolic murmur not previously heard, and a precipitous change in the patient's general condition. A patient with known septal infarction suddenly becomes much worse, with renewal or aggravation of the anginal pain, shortness of breath, dyspnea at rest, cyanosis, congestive heart failure

and peripheral vascular collapse. The prognosis is uniformly bad, and treatment is futile.

WENDKOS

ELECTROCARDIOGRAPHY

Burstein, J.: Myocardial Infarction. Acute Course and Prognosis in One Hundred and Twenty-seven Cases of Varied Extent and Localization Electrocardiographically Determined with the Aid of Multiple Unipolar Leads. Acta med. Scandinav. **147:** 5 (Supplement 285), 1953.

The author has correlated the course and prognosis with localization by electrocardiographic methods in 127 patients with acute myocardial infarction studied at the Maria Hospital from 1949 to 1952. It was observed that the course was milder and the prognosis during the follow-up period of twelve months more favorable in patients with subtransmural infarcts (probably subepicardial in the anterior wall) than with infarcts of transmural extent. The acute course seemed more favorable in posterior transmural than in anterior transmural lesions, possibly because the former usually were less extensive. Only a single case of subendocardial infarction was encountered and the course and prognosis in that patient were favorable. The prognosis in the first year after the onset was more favorable in anteroseptal transmural infarcts than in large anterior transmural infarcts, although congestive heart failure occurred with almost equal frequency in the two groups. The author has found that septal involvement does not affect the prognosis unfavorably except as it may be an additional indication of great magnitude of the area of infarction. Furthermore, the prognosis did not appear to be worse in patients with extensive septal infarction causing bundle branch block than in those with extensive infarction in other parts of the heart. However, total atrioventricular block or the occurrence of serious arrhythmias, especially serial ventricular extrasystoles, does tend to worsen the prognosis. Complete clearing of the changes in the RS-T segment and the QRS complex tended to occur in subtransmural infarctions but when the lesion was transmural in extent the changes were far more persistent. The acute course and prognosis was very favorable in those cases showing complete clearing of the abnormalities in the QRS complexes and/or the RST segments over the period of twelve months from the time of the initial attack.

ROSENBAUM

Hellerstein, H. K., Shaw, D. and Sano, T.: Dissection of the Vectorcardiogram: Differential Vectorcardiography. Am. Heart. J. **47:** 887 (June), 1954.

Vectorcardiograms are usually obtained by reconstruction from orthogonal leads or by synthesis by a cathode-ray oscilloscope. The former method is tedious and requires multichannel recorders. The vectorcardiograms obtained with the cathode-ray oscilloscope have in general not been satisfactory because of photographic difficulties in distinguishing the individual characteristics of the component four loops (P, QRS, Ta and ST-T loops), particularly the ST-T and P loops.

In view of the importance of obtaining separated components of the vectorcardiogram, the authors developed "an electrical dissector" (selective blanker or unblanker) which can be used with commercially available apparatus, cathode-ray oscilloscopes, preamplifiers, ordinary camera, and a single-channel direct-writer. Detailed diagrams and descriptions of the circuits and equipment were presented. Several examples of differential vectorcardiograms were shown with simultaneous electrocardiograms.

MAXWELL

Slapak, L. and Hermanek: Coronary T waves in the Electrocardiogram caused by Circumscribed Fatty Degeneration of the Myocardium. Cardiologia **24:** 259 (Fasc. 5), 1954.

A case is described of a 48 year old man with chronic glomerulonephritis, uremia, and congestive heart failure, in which coronary T waves were recorded in the electrocardiogram pointing to a lesion of the posterior wall. At autopsy, the only alteration in this region was an area of pronounced fatty degeneration. The authors believe that this was the cause of the marked electrocardiographic changes and discuss in detail the differential diagnosis from other electrocardiographic alterations of more common etiology.

PICK

HYPERTENSION

Taylor, R. D., Corcoran, A. C. and Page, I. H.: Increased Cerebrospinal Fluid Pressure and Papilledema In Malignant Hypertension. Arch. Int. Med. **93:** 818 (June), 1954.

A study is reported of the association of cerebrospinal fluid pressure (CSFP), diastolic arterial pressure, and papilledema, based on more than 400 measurements of CSFP made in 200 patients with hypertensive disease, 100 of whom manifested papilledema. No association between diastolic pressure and CSFP was found in hypertensive patients without papilledema; in hypertensive patients with papilledema the statistically significant correlation was not sufficient to indicate causation, since patients without papilledema showed elevated CSFP and patients with severely elevated diastolic pressures were often free of papilledema.

Similarly, in serial observations on patients whose papilledema altered in severity, remitted, or recurred, no close association between these changes and CSFP could be shown. Serial observations of CSFP in individual patients show considerable fluctuations in this function, independent of diastolic pressure. Papilledema and increased CSFP, like hypertensive encephalopathy, are to be regarded as specific manifestations of hypertensive disease, unrelated as to cause and effect.

BERNSTEIN

Howard, J. E., Berthrong, M., Gould, D. M. and Yendt, E. R.: Hypertension Resulting from Unilateral Renal Vascular Disease and its Relief by Nephrectomy. Bull. Johns Hopkins Hosp. **94**: 51 (Feb.), 1954.

The authors report in detail six patients with severe hypertension clearly secondary to impairment of blood flow to one kidney and with dramatic improvement following removal of the involved kidney. In four of the patients intravenous pyelography yielded normal findings; in the other two retrograde pyelography revealed a normal calyceal system although no contrast substance was demonstrated in the offending kidney. Two of the patients with normal intravenous pyelograms had histories compatible with recent renal infarction. (The younger of these patients was only 31 years old.) Both were suspected of having acute appendicitis at the time of the acute episode. In two other patients with normal intravenous pyelograms abdominal aortograms revealed stenosis or occlusion of the major renal artery. A potentially valuable observation is that of reduced excretion of urine and sodium by the involved kidney as compared with the normal despite bilaterally normal pyelograms. Two of the patients showed shrinkage of the offending kidney on abdominal x-rays or intravenous pyelograms taken a few months apart during which time hypertension had developed. Pathologically two showed extensive tubular atrophy throughout the culpable kidney; two showed wedge-shaped areas of infarction; two had a remarkably normal histological appearance except for remarkable hyperplasia of the juxtaglomerular body in one of these.

McKusick

PATHOLOGY & PATHOLOGIC PHYSIOLOGY

Saloni Kides, N.: Contribution to the Study of the Physiopathology of the Circulation in The Course of Surgical Intervention Involving the Lungs. Acta Cardiol. **9**: 235 (Fasc. 3), 1954.

In 20 patients submitted to pneumonectomy, blood volume, circulation time, venous pressure, and the electrocardiogram were recorded before and after surgery. Essential modifications were found in the first two determinations while changes occurring in the other two were not conclusive.

Following surgery the plasma volume may increase but the red cell volume and total blood volume are almost always reduced. The latter finding exemplifies the importance of the factor of hemorrhage, the significance of which has not yet been specified. Circulatory modifications after pneumonectomy do not differ from those encountered after other types of surgery. In particular, it would appear that the sudden blocking out of even half the pulmonary vascular field does not lead to specific hemodynamic alterations.

Pick

Bouchard, F. and Cornu, C.: A Study of Right Ventricular and Pulmonary Arterial Pressure Curves in Pulmonic Stenosis. Arch. d. mal. du coeur **47**: 417 (May), 1954.

The authors studied the contour of pressure curves of the right ventricle, and at different levels of the pulmonary artery in 115 cases of pulmonary stenosis with and without intact ventricular septum. The material consisted mainly of curves recorded during cardiac catheterization but in some cases was obtained by direct puncture during surgery. In several instances the left ventricular cavity was catheterized through a coexistent inter-atrial communication and the configuration of right and left ventricular pressure curve could be compared.

Two consistent patterns of right ventricular pressure curves could be established which depend on the presence or absence of an overriding aorta. In the latter case the curve has a peaked symmetrical appearance without a systolic plateau with a slow ascending limb. In the former, the curve is asymmetric with a more rapid ascent and a plateau at its top, and thus closely resembles the appearance of normal left ventricular curves.

An analysis of the records of the low pulmonary arterial pressure revealed differences depending on the type of stenosis and the area of recording. In valvular stenosis, with a small circular opening on top of the fused leaflets, the curves recorded close to the stenosis, in the area of a palpable thrill, show a small systolic elevation followed by a deep systolic dip. The latter disappears when the catheter is advanced to a more peripheral position in the pulmonary artery, and is not present above the valve when the obstacle is located below the valvular stenosis. This was found whenever the systolic right ventricular pressure exceeded 60 mm Hg. It was also recorded when valvular and infundibular stenosis were associated as occurs in some cases of tetralogy. The two features of pulmonary valvular stenosis, the peaked pressure curve ahead of, and a systolic dip beyond the stenosis, could be reproduced in a hydraulic model. On this basis the authors conclude that the type of pulmonary stenosis in a given patient can be predicted from the contour of the recorded pressure curves.

Pick

Neri, R. J., Villagordoa, G., Moros, G. and Dorbecker, N.: Pulmonary Circulation Time, Elbow-Left Ventricle and Elbow-Right Ventricle Circulation Times, Obtained by Means of Fluorodensography with Radiopaque Substance. Am. Heart J. **47**: 818 (June), 1954.

The authors studied the circulation time from the right elbow to the right ventricle, right elbow-left ventricle, and pulmonary circulation time by fluorodensography with radiopaque substance (diodrast). By simultaneous fluoroscopy and electrokymography, it was shown that the introduction of an opaque substance into the blood stream increases

the amplitude of the ventricular volume curves, which is synchronous with the arrival of the substance to the chamber under study.

The circulation times of nineteen normal adults were as follows: elbow-left ventricle, 5.61 seconds (mean value); elbow-right ventricle, 1.63 seconds; pulmonary circulation time, 3.98 seconds. In a patient with an aneurysm of the pulmonary artery the circulation time from elbow to left ventricle was 41 seconds; elbow-right ventricle, 4.2 seconds; and the pulmonary circulation time, 36.8 seconds. The equipment utilized is described in detail as well as the standardization of the various instruments and the technique for the recording and interpretation of the tracings.

MAXWELL

Kaplan, E., Puestow, R. C., Baker, L. A. and Kruger, S.: Blood Volume in Congestive Heart Failure as Determined with Iodinated Human Serum Albumin. Am. Heart J. **47**: 824 (June), 1954.

Blood volume was determined with iodinated human serum albumin in 32 patients with congestive heart failure of varying etiology; repeat determination was made in 25 of the patients after treatment leading to compensation. Total blood volume was elevated above normal in all the decompensated patients, with total packed red cell volume more markedly elevated than plasma volume. There was no consistent relationship of degree of increase in volume to the etiology of the heart disease; in general, the most severely decompensated patients showed the highest volumes. In response to therapy the plasma component was more labile and decreased more rapidly than the cellular component. Hematocrit values increased with therapy. During recovery from congestive heart failure the rate of apparent destruction of erythrocytes exceeded, in some instances, the expected calculated rate of destruction.

MAXWELL

Michelazzi, A. M.: Angiomatous Type Changes in the Emphysematous Lung and Their Probable Functional Significance. Cardiologia **24**: 210 (Fasc. 4), 1954.

Histopathologic studies are presented of lungs of patients who died from pulmonary emphysema and in which angiomatous alterations were found. In these vascular structures which involved both arteries and veins, the muscular tissue was largely replaced by fibrous tissue and the vessel walls varied greatly in thickness so that a free intercommunication between these vessels was suggested. It would appear that these lesions are related to the dynamic alterations occurring in the pulmonary circulation of patients with emphysema, and that they may play an important role in the pathogenesis of cyanosis.

PICK

Epstein, B. E. and Li, T. H.: The Determination of Cardiac Output by the Dye Dilution Method: Modifications, Comparison with the Fick Method and Application During Anesthesia. Anesthesiology **15**: 217 (May), 1954.

Since the determination of the cardiac output by the Fick method during general anesthesia is technically difficult and liable to numerous errors, the authors investigated the dye dilution technique. Determination of cardiac output was performed in dogs under pentobarbital anesthesia. In addition, duplicate dye dilution cardiac output determinations were obtained in six human beings during pentothal anesthesia, twelve cardiac outputs were determined in ten patients during the sedated state and twenty determinations were obtained in ten resting patients. The technical method employed in the dye dilution method is described and several modifications in the dye injection aspect are presented.

The cardiac outputs in the dog experiments by the dye injection method as compared to the values obtained by the Fick method were in agreement with the results reported from other laboratories. In most instances the values of the cardiac index by the dye method were lower than those obtained by the Fick method. The authors explain the discrepancy as being due in part to the different sources of error inherent in each method and also to the fact that the two methods do not estimate exactly the same circulatory factors. The mean cardiac index in dogs is 4.57 ± 0.29 L./min./m.^{2} (Fick) and 4.31 ± 0.26 (dye). The standard deviation of the difference of the two methods is 12.7 per cent. The precision of the dye injection method in humans is 2.44 per cent. The mean cardiac index during the postsedated state in human beings was found to be 3.29 ± 0.127 L./min./m.^{2}. No statistical difference between the cardiac output obtained during the postsedated state and during thiopental hypnosis was found. On this basis the authors propose that since a steady basal state can be maintained by the slow intravenous administration of 0.2 per cent thiopental, this drug be utilized to obtain resting values of cardiac output.

The dye method for the measurement of cardiac output has many advantages over the Fick method and is useful in determining the cardiac output during general anesthesia in human beings.

SAGALL

Björk, V. O., Malmström, G. and Uggla, L. G.: Left Atrial and Pulmonary "Capillary" Pressure Curves during Valsalva's Experiment. Am. Heart J. **47**: 635 (May), 1954.

Simultaneous measurements of the left atrial and pulmonary "capillary" pressures were made during the Valsalva maneuver in nine patients with mitral valve disease. In every instance the shape of the pulmonary "capillary" curve paralleled that of the left atrial pressure curve both during and after forced expiration.

In both curves the level of the pressure plateau was somewhat lower at the end of the maneuver than at the beginning; this fall in pressure was presumably due to the arrest of blood in the venous system and a consequent reduction in blood flow through the lungs. A marked decrease in the amplitude of peak 7 (representing opening of the mitral valve) during forced expiration was recorded in all but one of the patients; in this patient mitral regurgitation was suspected. After the end of forced expiration the pressure fell abruptly to below the resting values. This was followed by a rapid increase and an overshoot above the control values. This overshoot phenomenon was attributed to the sudden increase in pulmonary blood flow following release of the blood pooled in the venous system during the Valsalva maneuver.

MAXWELL

Lawson, H. C., Shadle, O. W., Coleman, E. S. and Holtgrave, D. E.: A Comparison of Intracardiac and Intravenous Injections for the Measurement of Cardiac Output by the Dilution Technic. Circulation Research **2**: 251 (May), 1954.

Using radioactive phosphorus ($H_3P^{32}O_4$) and the dye T1824 as labels, simultaneous injections were made into the right ventricle and into a peripheral vein of dogs, and cardiac output was calculated from the individual flow-dilution curves. When a discrepancy beyond the range expected from the use of the two labels occurred, the output from the central injection was always the larger.

If two successive injections were made into the ventricle at intervals approximating the delay in formation of the peripheral curve, the delayed curve frequently yielded a reduced value for cardiac output closely comparable with the reduction obtained with peripheral injections. Although possible error due to undetected recirculation could not be excluded, the data suggested that the reduced cardiac output with peripheral injections was attributable to a reduction in cardiac output during the procedure due to progressive blood loss in sampling.

MAXWELL

Kjellberg, S., Lind, J., Lonroth, H. and Rudhe, V.: Variations in Heart Volume in Normal Children of School Age. Acta Radiol. **41**: 441 (May), 1954.

This study concerns the statistical correlation that exists between the heart volume as performed by the method of Larsson, Kjellberg and associates and the surface area of school age children as calculated from height and weight by Du Bois.

The distribution around the regression line lies between 12 and 13 per cent. The authors conclude that at for practical purposes normal heart volumes lie within plus or minus 25 per cent of the values obtained by calculation of the body surface. The probability of a given heart volume being normal may vary as much as 40 per cent.

SCHWEDEL

Scherf, D. and Blumenfeld, S.: Mechanism of Auricular Flutter Caused by Crushing and Electrical Stimulation. Cardiologia **24**: 193 (Fasc. 4), 1954.

The authors repeated recent experiments of Rosenblueth and Garcia Ramos in order to test their conclusions concerning the mechanism of auricular flutter. Flutter was initiated in the atria of dogs by electrical stimulation following crushing of the intercaval region, or of an area near the sinus node. A ligature applied across the pathway of a supposed circulating wave failed to stop the auricular flutter in 11 experiments. Cooling of the sinus node, on the other hand, brought flutter to a standstill in every instance. On this basis the authors conclude that this type of experimental auricular flutter—like the aconitin induced flutter—is not caused by a circus movement, but is the consequence of rapid firing of a singe ectopic focus.

PICK

Shepherd, J. T., Burchell, H. B. and Wood, E. H.: Demonstration of Variations of Aortic to Pulmonary Artery Flow During the Cardiac Cycle In A Patient With A Patent Ductus Arteriosus and Pulmonary Hypertension. Proc. Staff Meet. Mayo Clinic. **29**: 301 (May), 1954.

A method is described for the withdrawal of blood samples from the heart and great vessels of man during any phase of the cardiac or respiratory cycle. By means of this method, cyclic variations in the oxygen saturation of blood in the pulmonary artery associated with the heartbeat in a patient with patent ductus arteriosus with a bidirectional shunt is demonstrated. In this patient, blood withdrawn from the pulmonary artery during the systolic phase of the electrocardiogram was higher in oxygen saturation than that withdrawn during diastole. It is concluded that the rate of left-to-right blood flow through the ductus during systole exceeded that occurring during diastole.

The implications of this finding in relation to probable systematic errors in determination of pulmonary blood flow by conventional application of the direct Fick principle under this circumstance are discussed. No differences were demonstrated during the expiratory and inspiratory phases of the respiratory cycle.

SIMON

Ditzel, J. and Sagild, A.: Morphologic and Hemodynamic Changes in the Smaller Blood Vessels in Diabetes Mellitus. II. The Degenerative and Hemodynamic Changes in the Bulbar Conjunctiva of Normotensive Diabetic Patients. New England J. Med. **250**: 587 (Apr. 8), 1954.

The study employed the stereoscopic dissecting microscope in the study of the blood vessels and circulating blood of the conjunctiva. Two hundred and forty selected patients were observed, 150 with and 90 without diabetes. The ages of the two groups

were quite comparable and all subjects had normal blood pressures. The most consistent change in the diabetic subjects was the aggregation of blood cells with loss of normal, "streamlined" hemodynamics in the smaller vessels. So far as vascular changes were concerned, the differences between diabetic and non-diabetic patients were most pronounced in the younger age groups. The primary and most typical vascular lesions were in the capillaries and venules with elongation of the venous portion of the capillaries and distention of the venules. In this respect the vascular pattern differed from that of essential hypertension in which the typical lesion is arteriolar constriction. The aggregates noted in the smaller vessels were not a rouleau formation but an irregular clumping, primarily of the red cells. It is felt that the relation between the metabolic disorder and the vascular changes is not a causal one but that both reflect some unknown underlying disturbance. The unexpectedly frequent occurrence of edema, "hyaline" infiltration and punctate hemorrhages in the conjunctiva associated with only minimal hemodynamic changes is considered by the authors to suggest certain primary changes in the membrane function of the capillaries in diabetes.

ROSENBAUM

Capeller, D.: Mechanism of Mutual Dependence of Lung and Peripheral Circulations. Helvet. physiol. acta **12:** 23 (May), 1954.

An experimental method is described to render right ventricular inflow independent from left ventricular output. When this method was used to investigate the interrelationship of pulmonary and systemic circulations in the cat, it was found that the minute volume of the right heart remained unchanged even when the left ventricular output increased by 40 per cent. It would therefore appear, that in the cat, under experimental conditions, right ventricular efficiency is independent from the hemodynamics of the left ventricular and under the regulation of other mechanisms.

PICK

Ditzel, J.: Morphologic and Hemodynamic Changes in the Smaller Blood Vessels in Diabetes Mellitus. I. Considerations Based on the Literature. New England J. Med. **250:** 541 (Apr. 1), 1950.

The author has made an extensive review of the literature concerning the changes in the smaller blood vessels in diabetes. This review was undertaken prior to initiation of a project concerned with the study of the smaller blood vessels and arterial blood flow in the bulbar conjunctiva. The author concludes that in diabetes mellitus the fundamental pathological change is in the endothelial cell and basement membrane. In these vessels there can be seen a proliferation of the endothelium and an accumulation of hyaline nodules and hyaline thickening as in the kidney glomeruli and in the capillary basement membrane in the retina. An increased fragility and possibly an increased permeability of the capillaries is also an important functional disturbance. In the smaller blood vessels of the conjunctiva in diabetic persons, there is often aggregation of the blood cells and the appearance of clumps of cells which tend to plug the tips of the arterioles transiently.

ROSENBAUM

Nahas, G. G., Josse, J. W., and Muchow, G. C.: Influence of Acute Hypoxia on Peripheral and Central Venous Pressures in the Non-Narcotized Dog. Am. J. Physiol. **177:** 315 (May), 1954.

Effective pressures in superior and inferior venae cavae were unchanged when non-narcotized dogs breathed 8 per cent oxygen in nitrogen. Venules increased 2.3 mm. Hg and small veins 1.4 mm. Hg in a similar experimental condition. The pressure gradient between venule and vein increased during hypoxia. This increased gradient may be related to the rise in cardiac output during hypoxia.

OPPENHEIMER

Meiners, S.: Methodical Contribution to the Determination of Pulse Wave Velocity. Ztschr. f. Kreislaufforsch. **43:** 297 (May), 1954.

The present methods of determination of pulse wave velocity with the help of sphygmomanometry are inadequate and in many cases inapplicable. The time of delay between the central and peripheral pulse wave, which is the basis of all calculations, varies when pulses are recorded with manometers of different sensitivity. The difference is only small in normotensives, but may attain 100 per cent in hypertensive patient. Two systems with different sensitivity respond almost simultaneously when used close to the heart but respond with a considerable time difference when applied remote from the heart.

These findings in man can be reproduced experimentally in models using elastic tubes. The types and causes of deformation of pulse waves in such experiments, and their relation to blood pressure recordings are discussed. Some of the difficulties in precise recording could be overcome by the use of standardized manometers provided that an agreement could be reached concerning the exact definition of the term "pulse wave velocity."

PICK

Short, D. S.: The Syndrome of Alternating Bradycardia and Tachycardia. Brit. Heart J. **16:** 208, (Apr.), 1954.

Four individuals are described who displayed marked sinus bradycardia alternating with auricular tachycardia or flutter. Two had mitral valve disease, one had aortic valve sclerosis and the fourth had no cardiac lesion. Minor syncopal attacks occurred during phases of bradycardia and palpitation during bouts of tachycardia. Occasionally, Stokes-Adams attacks were present. Digitalis proved to be the best remedy during paroxysms of tachycardia. In three patients who were followed for five years the

syndrome remained unchanged in two and was abolished in one who developed permanent auricular fibrillation. The mechanism for this arrhythmia is unknown but it is postulated that there is a subnormal activity of the sino-auricular node.

SOLOFF

Bloorner, W. E., Stern, H., and Liebow, A. A.: Application of Induced Pulmonary Arterial Collateral Circulation as Collateral Supply to the Heart. Proc. Soc. Exper. Biol. & Med. **86:** 202 (May), 1954.

In seven dogs the left pulmonary artery was ligated; the pericardium was stripped from the anterior and left lateral surface of the heart, and the lung surface and exposed myocardial surfaces sutured together after the opposing surfaces were cauterized with silver nitrate. Nine to 20 weeks after operation the animals were sacrificed and vinylite plastic casts were made of the coronary and pulmonary vessels and bronchial tree. In five of the seven animals abundant communications had developed between the coronary and bronchopulmonary arterial circulations. It is thought, but not proven, that the blood flow is from the coronary vessels to the bronchopulmonary circulation. Further experiments are to be reported to determine the direction of flow and to see the effects of interrupting flow in the coronary vessels.

HARVEY

Kowalski, H. J., Abelmann, W. H., and McNeely, W. F.: The Cardiac Output in Patients with Cirrhosis of the Liver and Tense Ascites with Observations on the Effect of Paracentesis. J. Clin. Invest. **33:** 768 (May), 1954.

Thirteen patients with portal cirrhosis and tense abdominal ascites were studied. There was no evidence of organic heart or lung disease. This group was compared with patients with cirrhosis without evidence of ascites or edema but otherwise comparable and studied in an identical manner.

In general, patients with ascites showed higher mean values for the cardiac output than patients without ascites but the differences were not significant. In both groups of patients the cardiac output was never low—it was either normal or high. The resting cardiac output remained essentially unchanged after abdominal paracentesis. In no instance did the cardiac output decrease, but in two cases there was a transient rise immediately following this procedure.

The authors conclude that tense ascites is not an important determinant of the cardiac output in patients with cirrhosis at rest and recumbency.

WAIFE

Lewis, H. P.: Cardiac Involvement in Hemochromatosis. Am. J. M. Sc. **227:** 544 (May), 1954.

In hemochromatosis with cardiac involvement the heart becomes diffusely enlarged and a rapidly progressive myocardial failure eventually follows. Both sides of the heart appear to be simultaneously involved. Edema is a prominent finding; murmurs are usually absent; no significant blood pressure changes are noted. There is a high incidence of arrhythmias and conduction defects in these patients. Electrocardiographic changes are not striking in degree and consist of low voltage in the QRS complexes and T wave alterations in addition to the arrhythmias. The clinical diagnosis of heart failure due to this cause is not difficult if it occurs in association with other classical evidences of hemochromatosis such as hepatic cirrhosis, skin pigmentation and diabetes. Liver biopsy, bone marrow biopsy, determination of serum iron or degree of saturation of iron binding protein are helpful in diagnosis. Cardiac failure in these cases may be related to biochemical changes in important enzyme systems by the excess iron found within the heart. Treatment of heart failure due to hemosiderosis is usually unsatisfactory. Repeated bleeding to remove excess iron stores may be a way to reduce the severity of the changes found in this disease.

SHUMAN

Prinzmetal, M., and Kennamer, R.: Emergency Treatment of Cardiac Arrhythmias. J.A.M.A. **154:** 1049 (Mar. 27), 1954.

It is pointed out that the majority of cardiac arrhythmias can be controlled by proper use of the digitalis glucosides, quinidine, and procaine amide (Pronestyl), carotid sinus massage, and sedation. Since the clinical severity of an arrhythmia is usually proportional to the disturbance in the ventricular rate, emergency treatment is designed to normalize this rate even though the arrhythmia persists. Paroxysmal auricular tachycardia can frequently be terminated by carotid sinus massage. It is brought out that this is not simple pressure over the carotid sinus but a regular sustained massage of this area done first on one side, then on the other, but never on both sides simultaneously. Auricular tachycardia in elderly patients should be treated with digitalis and quinidine given intramuscularly. Rapid auricular tachycardia in infants may cause congestive failure and thus require immediate intravenous administration of digitalis. Auricular flutter is usually associated with organic heart disease and digitalis is indicated if the ventricular rate is rapid or if evidence of heart failure is present. Auricular fibrillation with rapid ventricular rate is treated by parenteral administration of digitalis. Attempts to induce conversion with quinidine and/or procaine amide may be advisable in certain instances. Ventricular tachycardia is one of the most serious cardiac arrhythmias and requires prompt therapy. Parenteral administration of quinidine and/or procaine amide is the treatment of choice. Cardiac arrest management is extremely difficult as many patients do not respond to routine therapeutic measures. Epi-

nephrine, isopropylarterenol hydrochloride, and hydroxyamphetamine hydrobromide may be useful in treatment of syncopal attacks resulting from asystole in patients with complete heart block or with carotid sinus hypersenitivity. Such attacks resulting from paroxysmal ventricular fibrillation in patients with complete heart block occasionally can be terminated with atropine or prevented with isopropylarterenol and hydroxyamphetamine. Quinidine and procaine amide are contraindicated if heart block is present; they may be used to control paroxysms of ventricular fibrillation in patients with previously normal auriculoventricular conduction. Cardiac standstill or ventricular fibrillation may cause permanent damage to the cerebral cortex within 3 to 4 minutes. Lifesaving measures are the use of the external electric stimulator and direct cardiac massage. In ventricular fibrillation, the heart may be oxygenated by direct cardiac massage, after which an electric defibrillator is used to restore sinus rhythm. Among the reports of cases illustrating the need for specially devised therapy, one case concerns the successful use of corticotropin (ACTH) to terminate heart block following myocardial infarction. This should be tried in such instances when usual methods of therapy fail as the heart block may be due to inflammation of the auriculoventricular node and bundle of His which can be suppressed with the drug.

KITCHELL

Freeman, R. U., Berger, L. M., Cohen, S. and Selle, W. A.: Major Neuropsychiatric Residuals Following Resuscitation from Cardiac Arrest. J.A.M.A. **155:** 107 (May 8), 1954.

Resuscitation for cardiac asystole is being performed with increasing frequency. Improvements in rescue technique and in postoperative care will account for an increasing number of survivors. Some of these cases will have sustained irreversible damage to higher nervous centers. Such damage includes loss of recent memory, inability to relearn, ataxias, emotional lability, and intellectual impairment with loss of integrative capacities. Three cases are reported with such damages remaining 18–36 months after the event.

KITCHELL

Folkow, B. and von Euler, U. S.: Selective Activation of Noradrenaline and Adrenaline Producing Cells in the Cat's Adrenal Gland by Hypothalamic Stimulation. Circulation Research **2:** 191 (May), 1954.

Hypothalamic stimulation in anesthetized cats induced secretion of adrenaline and noradrenaline from the adrenal gland in varying proportions depending on the location of the stimulus. From the selective activation of the secretion, it is inferred that adrenaline and noradrenaline producing cells are innervated by separate fibers with a different hypothalamic representation. Nicotine stimulation increased the adrenaline percentage of secretion in 8 of 9 cases, the average increasing from 22 to 3[illegible] per cent.

MAXWELL

PHARMACOLOGY

Rey, C. and Pattani, F.: The Treatment of Cardiovascular Affections by a Total Heart Extract. Acta Cardiol. **9:** 221 (Fasc. 3), 1954.

Recent experimental investigations have shown that Recosen, a total heart extract, increases coronary flow and reduces the oxygen needs of the cardiac cell. The clinical effects of the substance were tested in 32 cases of angina pectoris, 20 cases with heart failure, and 6 cases with intermittent claudication. In two-thirds of the cases with angina, oral and intravenous Recosen medication had favorable results but it was a failure in the presence of severe coronary disease, in angina associated with left heart failure or an aortic valvular lesion. In cases of congestive heart failure Recosen proved a valuable adjuvant to the conventional therapy. Its effects were less conclusive in the presence of auricular fibrillation. Recosen used over a protracted period of time can improve intermittent claudication and nocturnal pain due to arteriosclerotic impairment of the circulation of the legs.

PICK

Alström, I.: Effect of the Digitalis Glucoside Digitoxin on the Phosphorus Metabolism in Heart and Liver of Rats, Measured by the Radioactive Phosphorus Isotope P_{32}. Acta med. Scandinav. **148:** 439 (Fasc. 6), 1954.

The author has used radioactive phosphorus P_{32} to study the effect of digitoxin upon the rate of phosphorus metabolism in the heart and liver of rats. Subtoxic doses of digitoxin increased the rate of phosphorus metabolism in the heart but left the liver unaffected. Toxic doses of digitoxin decreased the rate of phosphorus metabolism in the liver and left the heart unaffected. It is mentioned that this may be the basis for the therapeutic effect of digitalis in small doses and the toxic effect when larger doses are given.

ROSENBAUM

Moyer, J. H., Hughes, W. and Huggins, R.: The Cardiovascular and Renal Hemodynamic Response to the Administration of Reserpine (Serpasil). Am. J. M. Sc. **227:** 640 (June), 1954.

Reserpine, a pure alkaloid, obtained from *Rauwolfia serpentina* has been shown to have mild to moderate hypotensive activity. Observations were made in animals and humans on the cardiovascular and renal hemodynamic responses to this drug when administered intravenously and orally. Following intravenous administration of the drug to dogs, the cardiac output was either unchanged or decline[illegible]

slightly during the period of blood pressure reduction. Renal hemodynamics and electrolyte excretion rates were not significantly altered. In hypertensive patients, renal blood flow, glomerular filtration rates and renal excretion of water and electrolytes were not altered by intravenous administration or by oral administration for 3 months. There was no evidence of renal toxicity or depression of renal function. The drug was found to have a moderate potency in its ability to reduce the blood pressure both after intravenous or chronic oral administration.

SHUMAN

Friend, D. G., and Edwards, E. A.: Use of "Dibenzyline" As a Vasodilator in Patients with Severe Digital Ischemia. Arch Int. Med. **93:** 928 (June), 1954.

Dibenzyline (N-phenoxyisopropyl-N-benzyl- chloroethylamine hydrochloride) has been given orally to 23 patients suffering from digital ischemia. Several patients were carried through two winters. Results were uniformly good in patients suffering from Raynaud's disease, the patients finding that they could go through the cold months with comfort. Dibenzyline failed to relieve the one patient suffering from minor causalgia. The drug gave inconsistent results in patients suffering from disorders in which organic vascular occlusion predominates. It was, however, of value in relieving symptoms in two patients with occlusion of major arteries until collaterals could develop. The drug was given to two patients with residual activity after sympathectomy. In one with scleroderma the drug gave considerable relief, but in the second, suffering from arteriosclerosis, it corrected only excessive sweating.

BERNSTEIN

Stein, I. D. and Rose, O. A.: Treatment of Superficial Thrombophlebitis With Phenylbutazone (Butazolidin). Arch Int. Med. **93:** 899 (June), 1954.

Thirty-three patients with superficial thrombophlebitis due to various causes, many not responding to other forms of therapy, were treated with phenylbutazone (Butazolidin). They were ambulant and not restricted in salt, fluids, or diet. The drug was used for one week in the majority of cases in daily dosage of 300 to 600 mg. for a total dose of 3.0 to 3.5 gm.

In all patients there was rapid complete or partial regression of the vein inflammation. Phenylbutazone reduces the duration of bed rest, disability, and economic loss. As such, it is a useful adjunct in the treatment of thrombophlebitis. Because of the possibility of toxic effects on the bone marrow, gastrointestinal tract, skin, and other organs, every effort should be made to safeguard the patient by frequent examinations and blood cell count.

BERNSTEIN

Loffler, W., Essellier, A. F. and Forster, G.: Acetyl-Digitoxin. Clinical Observations on the Treatment of Patients with Advanced Congestive Heart Failure. Am. Heart J. **47:** 898 (June), 1954.

Acetyl-digitoxin, a glycoside obtained from *Digitalis lanata,* was tested in the treatment of 120 patients with severe cardiac failure of varying etiology. The effect of the glycoside was judged by the clinical picture, with daily checks of pulse rate, pulse deficit, blood pressure, respiratory rate, diuresis, body weight, and signs of congestion, as well as by repeated measurements of heart size, vital capacity, venous pressure and circulation time.

The drug reduced the heart rate considerably, had an excellent diuretic effect, and was well absorbed from the intestinal tract (rate of absorption: 67 per cent). It increased cardiac efficiency (positive inotropic effect), which manifested itself clinically by increasing abnormally low blood pressure, increasing pulse pressure, and also frequently by reducing the heart size and thus the amount of residual blood. Its action began within 20 to 30 minutes after intravenous injection and 2 to 4 hours after oral ingestion. Its effect lasted 9 days, with a daily elimination rate of 14 per cent. These properties place acetyl-digitoxin midway between digitoxin and the glycosides Digilanid and lanatoside C.

Acetyl digitoxin was well tolerated and had a large therapeutic margin, thus combining the efficacy of digitoxin with the lower toxicity of the glycosides prepared from *Digitalis lanata.* Because of its high rate of fixation, more persistent action, and cumulation, it is well suited for the maintenance treatment of patients with chronic cardiac failure.

MAXWELL

Moyer, J. H. and Snyder, H. B.: The Cerebral Hemodynamic Response to the Xanthine Compound, Parephyllin (Diethyl-aminoethyl Theophylline Hydrochloride). Am. Heart J. **47:** 912 (June), 1954.

Observations were made in one normotensive and six hypertensive patients on the cerebral hemodynamic response to Parephyllin, a soluble salt of theophylline which can be given in large doses orally and intramuscularly without causing local reaction. In contrast to aminophylline, Parephyllin does not reduce cerebral blood flow. Since this agent may relieve Cheyne-Stokes respiration much as aminophylline does, it seems likely that the mode of action for both drugs is by their direct stimulant effect on the respiratory center. The fact that the arterial oxygen increased in nearly all patients suggests that it may be an effective bronchodilator.

MAXWELL

Waser, P. G. and Volkart, O.: The Effect of Cardiac Glycosides upon Actomyosin. I. Measurements of Viscosity. Helvet. physiol. acta **12:** 12 (May), 1954.

The authors studied the influence of four different digitalis preparations upon the structure, viscosity

and thixotropy of solutions of actomyosin prepared from skeletal muscle of rabbits. The viscosity is reduced proportionally to the added amount of glycoside beginning at molar concentrations of 10^{-7}. Digilanid A showed the highest, and K-Strophantosid and Convallotoxin the lowest activity, while Gitalin was intermediate in its effect. The effect is abolished by addition of methanol, or ethanol, in small concentrations. The action of ATP and ATP-ase, and the viscosity of solutions of myosin is not changed by these glycosides.

PICK

Faber, V.: Anti-Streptococcal Hyaluronidase IV. Comparison of Anti-Streptococcal Hyaluronidase and Anti-Streptolysin-O in Sera from Patients with Rheumatic Fever, Glomerulonephritis, Tonsillitis and Rheumatoid Arthritis. Acta med. Scandinav. **147:** 299 (Fasc. 4), 1953.

This study is concerned with the results of comparative measurements of anti-hyaluronidase (ASH) and of antistreptolysin-O (AST). The patients studied included 100 with rheumatoid arthritis and 50 with chronic nephritis, 100 with acute tonsillitis, 50 convalescents from acute uncomplicated tonsillitis, 100 with acute rheumatic fever and 100 with acute hemorrhagic glomerulonephritis. Practically speaking, the ASH and AST titres in patients with rheumatoid arthritis, chronic nephritis and acute uncomplicated tonsillitis did not differ from those in normal sera. In the other groups of patients, a varying number showed elevated values. The two tests showed almost identical numbers of normal, dubiously elevated and elevated values within the different patient groups. During streptococcal diseases there was no correlation between the two antibodies. Generally speaking, variations in ASH values showed a better correlation with the clinical activity. The two tests are considered practically equally sensitive indicators of an immunization with hemolytic streptococci, although ASH values usually exceed the normal by a greater margin than do those of AST. It is suggested that the use of both tests side by side will increase the likelihood of demonstrating antibodies against hemolytic streptococci.

ROSENBAUM

Brod, J., Fejfar, Z., Fejfarova, M. H.: The Role of Neuro-Humoral Factors in the Genesis of Renal Haemodynamic Changes in Heart Failure. Acta med. Scandinav. **148:** 273 (Fasc. 4), 1954.

Observations of the effect of Dibenamine and Dihydroergotamine upon renal hemodynamics and function in relation to general hemodynamics were made in 4 normal subjects and 15 patients with heart failure at various stages. In the normal subject Dibenamine had no effect on renal vascular resistance in the early stage when extrarenal resistance had already become markedly reduced. As a result, as cardiac output fell, there was a fall in renal blood flow. In eleven patients with heart failure and in two normal females with marked anxiety throughout the experiment, renal vascular resistance fell and renal blood flow increased following Dibenamine. The changes in renal vascular resistance appeared to be independent of any changes in general hemodynamics, i.e., a transient increase in cardiac output and a decrease in peripheral resistance. The authors conclude that the increased renal vascular tone in heart failure may be reduced by a direct blockade of adrenergic impulses reaching those vessels while the renal vascular tone in normal persons remains practically unaffected. The pathological increase of renal vascular tone in failure is, to a great extent, of neurohumoral (adrenergic) origin and is thus of reflex origin, as is the increase in general arteriolar and venous tone. This has an adverse effect on renal function with consequent disturbed water balance and accumulation of salt and water in the body, even though it is of temporary benefit so far as maintaining an adequate blood supply to the heart muscle, brain and skeletal muscles.

ROSENBAUM

Jewell, P., Pilkington, T. and Robinson, B.: Heparin and Ethyl Biscoumacetate in Prevention of Experimental Venous Thrombosis. Brit. Med. J. **1:** 1013 (May 1), 1954.

The authors found that in rabbits in which chemical phlebitis was induced in the ear veins ethyl biscoumacetate ("Tromexan") was strikingly effective in preventing the formation of thrombi when the drug was given in doses comparable to those used in man. With heparin, on the other hand, there was no significant reduction in the incidence of thromboses.

MCKUSICK

Brown, Robert V., and Hilton, James G.: Cardiovascular Responses to Epinephrine Before and After Denervation of the Pressoreceptors. Am. J. Physiol. **177:** 303 (May), 1954.

Pressoreceptor reflexes are unable to moderate either the blood pressure level or the height of the rise caused by circulating epinephrine. After large doses of epinephrine the fall in pressure is the same whether pressoreceptors are present or not. Not only do pressoreceptors fail to shorten pressor responses but after large doses of epinephrine they may actually prolong the response. At moderate epinephrine levels pressoreceptors produce a bradycardia. When epinephrine doses are increased the pressoreceptors and this humoral agent combine to produce arrhythmias. The authors are of the opinion that in rage and anger the pressoreceptors do not moderate any hypertension which is present. The pressoreceptor reflexes are more important against hypotension than against hypertension.

OPPENHEIMER

Shuman, C. R., Learner, N. and Doane, J. H.: The Effect of Ganglion Blocking Agents in Congestive Heart Failure. Am. Heart J. **47**: 737 (May), 1954.

Autonomic blocking agents, tetraethylammonium bromide and hexamethonium bromide, were administered intravenously to a group of patients with congestive heart failure of various etiologies in an effort to evaluate their effect on the elevated venous pressure.

Both drugs caused a marked decrease in venous pressure simultaneously with arterial pressure, as well as an increased vital capacity in patients with heart failure. Significant clinical improvement with a reduction in the degree of dyspnea and orthopnea lasting from one to several days frequently followed the procedure: those with milder degrees of congestive heart failure experienced longer benefits. Measurements of skin temperature and digital blood flow revealed that the usual increase noted in non-failure patients was absent in most patients with congestive failure.

The reduction of venous and arterial pressures without evidence of increased cutaneous or digital flow suggests that a redistribution of blood volume has occurred by the release of vasoconstrictor reflexes, probably in splanchnic or muscular areas. The release of neurogenic reflexes increasing the arteriolar and venular tone will reduce the work load of the left ventricle and decrease the elevated venous filling pressures of the right heart. The use of autonomic blockade as a method of treatment for pulmonary congestion was shown to be effective.

MAXWELL

Leaf, A., Schwartz, W. B. and Relman, A. S.: Oral Administration of a Potent Carbonic Anhydrase Inhibitor ("Diamox"). I. Changes in Electrolyte and Acid-Base Balance. New England J. Med. **250**: 759 (May 6), 1954.

Careful balance studies were performed in 5 patients with congestive heart failure and one normal subject during the administration of Diamox. In two of the patients and in the normal control there was increased urinary excretion of sodium and potassium and hyperchloremic acidosis developed. The other three patients showed an increased excretion of potassium and a reduction in urine acidity but no loss of sodium. Hypokalemia or evidence of potassium deficiency did not appear. Excretion of nitrogen, phosphorus and organic acids was essentially unchanged. Despite continuous administration of the drug, urinary excretion reverted to the pattern of the control period although hyperchloremic acidosis persisted throughout the treatment period. The usefulness of the drug as a diuretic appears to be limited by the rapid development of unresponsiveness, even with intervals of one or two days between doses. It was of interest that no patient lost sodium without potassium and the range of potassium loss was the same in those who lost sodium as in those who did not. This suggests an initial preferential loss of potassium when hydrogen transport is inhibited in patients with congestive heart failure. Two patients were treated with mercurial diuretics to contrast their reaction with that of Diamox. Both patients had a diuresis of chloride, accompanied by sodium and a small amount of ammonium and a weight loss considerably greater than that produced by Diamox.

ROSENBAUM

Relman, A. S., Leaf, A., and Schwartz, W. B.: Oral Administration of a Potent Carbonic Anhydrase Inhibitor ("Diamox"). II. Its Use as a Diuretic in Patients with Severe Congestive Heart Failure. New England J. Med. **250**: 800 (May 13), 1954.

Diamox was given in a total of 28 trials to 26 patients with severe congestive heart failure with varying degrees of peripheral and pulmonary edema. All other diuretics were omitted for at least two days prior to the trial of Diamox and no treatment other than digitalis and salt restriction was employed concurrently. The drug was given orally, in varying dosage schedules, for 3 to 12 days. Approximately one-half of the patients failed to lose weight, the majority of the others had small diureses ranging from 2 to 6 pounds, and one patient lost 11 pounds over a period of nine days becoming edema free. The major side effect was drowsiness, which occurred in 9 patients. This occurred only in patients receiving more than 500 mg. of Diamox per day. The least favorable response occurred in azotemic patients. Many of the patients who failed to show appreciable diuresis when given Diamox responded satisfactorily subsequently when given mercurial diuretics, aminophyllin and ammonium chloride in combined therapy. The failure of these patients to respond satisfactorily to Diamox is said to be in sharp contrast with the effect of this drug in patients with congestive heart failure due to chronic cor pulmonale.

ROSENBAUM

Bedard, O.: Quinidine in the Treatment of Auricular Fibrillation. Am. J. M. Sc. **227**: 530 (May), 1954.

This report is based on observation of 67 cases of auricular fibrillation associated with congestive heart failure. The etiology of auricular fibrillation included arteriosclerotic, hypertensive, and rheumatic heart disease. Quinidine was administered orally by schedule starting with 0.2 gm. to determine sensitivity to the drug. Two patients were excluded from treatment because of severe reactions. Reversion to normal sinus rhythm occurred in 89 per cent of the cases. The highest rate of reversion was noted in the hypertensive group and the lowest in those with rheumatic heart disease. The latter group required the largest doses of quinidine. Complications

or side effects of treatment occurred in 42 per cent of the patients and in 11 per cent it was deemed advisable to stop therapy before reversion was accomplished. The presence of serious conduction defects is considered a contraindication to quinidine therapy. There were 4.5 per cent of these patients in whom death may have been precipitated by quinidine.

SHUMAN

Chotkowski, L. A., Powell, C. P. and Rackliffe, R. L.: Methoxamine Hydrochloride in the Treatment of Paroxysmal Superventricular Tachycardia. New England J. Med. **250:** 674 (Apr. 22), 1954.

The authors report in detail the treatment of three patients with paroxysmal supraventricular tachycardia with Methoxamine (beta-[2.5-dimethoxyphenyl] beta-hydroxyisopropylamine) chloride, a synthetic amine, given intravenously in doses of 5 to 20 mg. One patient who had a ventricular rate of nearly 300 per minute was in vascular shock when the drug was given. Reversion to normal rhythm occurred within 35 to 50 seconds. A brief period of asystole and in one case, auricular fibrillation, occurred at the cessation of the tachycardia. The mechanism of action of methoxamine hydrochloride is believed to be by vagal stimulation. In all cases the blood pressure was elevated briefly after the drug was given and stabilized at a normal level a few moments later. Three additional cases, treated successfully in the same way, are mentioned in an addendum. No comparison of the effectiveness of this drug with other measures is made.

ROSENBAUM

Foreman, H., and Trujillo, T. T.: The Metabolism of C^{14} Labeled Ethylenediaminetetraacetic Acid in Human Beings. J. Lab. & Clin. Med. **43:** 566 (Apr.), 1954.

Ethylenediaminetetraacetic acid has been found to be active as an anticoagulant and useful in treatment of heavy metal poisoning. This study was undertaken to establish dosage, route of administration, distribution, and fate of this drug in the human body. C^{14} labeled drug was used. Normal healthy young adult males served as subjects. The drug is poorly adsorbed from the skin and GI tract. The blood is cleared quickly of the drug. It is distributed fairly evenly in body water. It is not found in erythrocytes. It crosses the blood brain barrier very slowly. It is excreted almost entirely through the kidney both by glomerular filtration and tubular excretion. It can be administered both intravenously and intramuscularly. No studies on toxicity are reported except in two instances when it is said, "No unusual cardiovascular changes could be detected in blood pressure, pulse, and electrocardiogram."

HARVEY

Lehr, D., Chureg, J., and Milova, R.: Influence of Alpha-Tocopherol Upon Development of Cardiovascular Necrosis and Hypertension in the Rat. Proc. Soc. Exp. Biol. & Med. **85:** 615 (Apr.), 1954.

A study was done on albino rats to determine the influence of Vitamin E on the development of arteritis and hypertension induced by poisoning with sulfathiazole. Renal tubular block occurs followed in about 5 days by extensive vascular necrosis and hypertension. Studies were done to determine what effects excessive amounts of Vitamin E (10 mgm. per day) had on the lesions so produced. Studies were well controlled. Animals were maintained on their diets for three weeks before renal lesions were produced. Systolic blood pressures were recorded with aid of a photoelectric tensometer. Animals were sacrificed at varying times and careful microscopic examination made. The arteritis produced was not ameliorated by administration of Vitamin E. The distribution of lesions actually suggests that Vitamin E may influence location of lesions causing an increase in myocardium and aorta. Excess intake of Vitamin E did not alleviate the hypertension in the rats with arteritis, and it appeared to induce hypertension in several of the controls.

HARVEY

Goldbloom, R. B.: Renal Failure with Extreme Hyperpotassemia. Its Treatment with Exchange Transfusions. New England J. Med. **250:** 717 (Apr. 29), 1954.

The case of a 10 year old girl with subacute glomerulonephritis who died after 42 days of extreme oliguria and anuria is presented in detail. It is pointed out that the signs and symptoms of hyperkalemia are variable and unreliable, poorly correlated with the degree of hyperkalemia and, at times, almost indistinguishable from hypokalemia. In this case the electrocardiographic abnormalities were more profound than in any case thus far reported with survival. Yet the serum potassium level was not as high as that recorded in other cases showing less striking electrocardiographic changes. This lack of correlation is partly due to the fact that potassium is primarily an intracellular ion, yet other observers have pointed out variable correlations even with measurements of myocardial potassium. This case emphasized the point that potassium intoxication in renal insufficiency may occur with dramatic suddenness and without warning and that serial electrocardiograms offer the chief indication of the severity of myocardial involvement, once it is found that hyperkalemia is present. The use of hypertonic glucose solution together with insulin permits safe and rapid treatment of severe potassium intoxication because by this means there is an uptake and intracellular transfer of potassium in the process of glycogenesis. Repeated exchange transfusions were used wit

good though transient effect in the patient reported. Such therapy offers a simpler technique than elaborate dialyzing methods and also offers several advantages so far as correction of anemia, acidosis and electrolyte imbalance are concerned.

ROSENBAUM

Mackay, R. S.: Ventricular Defibrillators. J.A.M.A. **154:** 1421 (Apr. 24), 1954.

The only acceptable method for stoppage of ventricular fibrillation is the application of a momentary intense electric shock to the heart. Recently the critical property of such a shock has been determined and it must include a specified minimum energy. The absolute minimum acceptable voltage was found to be 55 volts and the resulting current was one ampere. The time required is 0.065 second. In the range of current that will defibrillate one should use slightly more than the shortest time that will deliver the required minimum energy (of the order of magnitude of 4 joules), and add a second shock or increment if necessary. A simple device that makes a satisfactory defibrillator can easily be built. The usual power source fortuitously delivers just about the proper voltage for open chest defibrillation and a judiciously selected fuse will automatically abruptly open at the end of between 0.1 and 0.5 seconds. It is desirable when using fuses that the plug be inserted in the wall so that the fuse is in the ungrounded or hot side of the powerline. If two fuses are desired they should be placed in series in the ungrounded side. Such fuses have the interesting property of automatically slightly increasing the time if the current is slightly low. The operator can receive a momentary shock from any unit not containing an isolation transformer when he has simultaneous contact with the patient and the ground during the impulse (unless he is wearing intact rubber gloves).

KITCHELL

Black, D. A. K. and Mills, J. N.: Nocturnal Electrolyte Excretion After Oral Administration of Sodium and Potassium Chloride and Bicarbonate. Clin. Sc. **13:** 211 (May), 1954.

The effects of sodium and potassium chloride and bicarbonate in 50 mEq. doses on nocturnal electrolyte excretion were determined in five normal subjects. Hydrion outputs were reduced by potassium and by bicarbonate ions, with additive effects; but not by sodium chloride. Potassium was found to have a much greater influence on electrolyte output than sodium administration. Potassium salts increased the excretion of potassium, and even more of sodium. It appears that a high rate of potassium excretion depresses hydrogen excretion and vice versa. This is in line with the suggestion that there is a reciprocity between the amounts of potassium and hydrogen exchanged for sodium in the distal tubule. Apparently the renal response to small electrolyte loads is mediated through adjustments in the cation exchange in the renal tubules.

ENSELBERG

PHYSIOLOGY

Gundersen, K., Bradley, R. F. and Marble, A.: Serum Phosphorus and Potassium Levels After Intravenous Administration of Glucose. Their Use as Diagnostic Acids in Diabetic and Nondiabetic Subjects With and Without Liver Disease. New England J. Med. **250:** 547 (Apr. 1), 1954.

This report is concerned with observations of the blood sugar, serum inorganic phosphorus and serum potassium levels obtained during glucose tolerance tests in nondiabetic persons and patients with slight alterations in carbohydrate metabolism. Some persons in each group also had liver disease. Eleven normal volunteers and 41 patients were studied. There was no significant difference in the average maximum decrease in serum inorganic phosphorus and the ranges of values for the various groups showed a large overlap. There were also no distinctive differences in the patients with liver disease when they were taken as a whole. The decreases in serum potassium during the glucose tolerance tests were also practically identical in the various groups. The authors conclude that the maximum fall of phosphorus during a glucose tolerance test cannot be depended upon to differentiate so-called hepatic storage insufficiency (over-production of glucose by the liver) from true diabetes mellitus (peripheral underutilization of glucose).

ROSENBAUM

Bing, R. J., Siegel, A., Ungar, I. and Gilbert, M.: Metabolism of the Human Heart. II. Studies on Fat, Ketone and Amino Acid Metabolism. Am. J. Med. **16:** 504 (Apr.), 1954.

Using the technic of coronary sinus catheterization for in vivo study of the metabolism of the heart in man, the authors demonstrate that the human heart muscle utilizes considerable quantities of noncarbohydrate substances such as fatty acids, ketone bodies and amino acids. The heart was found to extract considerable amounts of these non-carbohydrate foodstuffs. Myocardial extraction ratios of fatty acids were particularly great after a high fat intake, suggesting storage of fat in the heart muscle. A negative correlation between myocardial carbohydrate and ketone utilization was observed. This finding is considered in accord with the theory of substrate competition for available oxygen. During infusion of amino acids the rise in arterial amino acid concentration produced a disproportionate increase in their myocardial extraction and a considerable increase in glucose extraction by the heart. Statistical analysis of the data revealed a large scatter in almost all observations. It seems likely

that this was the outcome of physiologic variations resulting from differences in the metabolic needs and requirements of the heart.

HARRIS

Lamfrom, H. Haas, E. and Goldblatt, H.: Studies on Antirenin. Am. J. Physiol. **177:** 55 (Apr.), 1954.

Hog renin was administered by intramuscular injection to hypertensive patients. A high concentration of antirenin developed in the serum. Pyrogenic, anaphylactic or hypotensive reactions were not produced by this pure renin. Although human and dog antirenin inactivated the renin of several species with varying degrees of effectiveness, neither neutralized the human renin. The rat quickly develops high titres of antirenin after small doses of renin. The presence of antirenin protects from the proteinuria which renin usually produces. This furnishes a useful method for assay of antirenin. Heterologous renin increases renin content of rabbit kidneys. Homologous renin depresses renal renin in this species. It was possible to dissociate the renin-antirenin complex in various ways. Antirenin could be recovered in an active form, however, renin could not be recovered in this state. The fact that antirenin can be dissociated and reactivated allows one antirenin molecule to react consecutively with several renin molecules. It is pointed out that this reaction and other familiar enzyme reactions have similar mechanisms.

OPPENHEIMER

Zatzman, M., Stacy, R. W., Randall, J. and Eberstein, A.: Time Course of Stress Relaxation in Isolated Arterial Segments. Am. J. Physiol. **177:** 299 (May), 1954.

Carotid arteries contain much parallel elastic elements. Umbilical arteries are almost entirely smooth muscle. When these two vessels are compared as to stress relaxation it appears that this phenomenon is related to the smooth muscle component of the artery. Stress relaxation is now exponential. When pressure or wall tension is plotted against the log of time, the time course was a straight line over two or more log cycles of time. Within ten seconds stress relaxation was about 80 per cent complete.

OPPENHEIMER

Nahas, G. G., Mather, G. W., Wargo, J. D. M. and Adams, W. L.: Influence of Acute Hypoxia on Sympathectomized and Adrenalectomized Dogs. Am. J. Physiol. **177:** 13, (Apr.), 1954.

The test objects were five unanesthetized sympathectomized dogs. When breathing 8 per cent oxygen in nitrogen, the changes in heart rate and cardiac output were smaller than in controls. Adrenalectomy in five other dogs eliminated these changes when they were studied under similar conditions.

OPPENHEIMER

Robertson, William Van B., and Dunihue, F. W.: Water and Electrolyte Distribution in Cardiac Muscle. Am. J. Physiol. **177:** 292 (May), 1954.

Adrenal insufficiency and salt depletion decreased intracellular sodium concentrations. However, excessive adrenal hormone, salt administration and perinephritis increased intracellular sodium. In each case the intracellular potassium was changed in a direction opposite to that for sodium. Changes in intracellular ions when considered in relation to extracellular changes were not compatible with unrestricted water movement. Calculated distributions of myocardial water in adrenal insufficiency point to an edema rather than an increase in intracellular water. This is different from currently accepted views.

OPPENHEIMER

RHEUMATIC FEVER

Kuhns, W. J. and McCarty, M.: Studies of Diphtheria Antitoxin in Rheumatic Fever Subjects: Analysis of Reactions to the Schick Test and of Antitoxin Responses following Hyperimmunization with Diphtheria Toxoid. J. Clin. Invest. **33:** 759 (May), 1954.

Studies from other laboratories have shown that the mean antibody response of a group of rheumatic fever patients to various antigens is greater than that of comparable patients with uncomplicated streptococcal disease. The authors wished to determine whether the hyper-reactivity of rheumatic subjects is limited to streptococcus antigens or is a reflection of a different mechanism

Two hundred and forty-five rheumatic and control subjects were studied in their skin-reaction response to Schick toxin and toxoid. In addition, antitoxin responses in 121 of these individuals, following a single booster dose of purified diphtheria toxoid, were measured. The data indicate that both qualitatively and quantitatively antitoxin responses to diphtheria toxoid are approximately the same in rheumatic and non-rheumatic individuals. The number of previous attacks of rheumatic fever also appeared to have no bearing upon the ability to form diphtheria antitoxin.

WAIFE

Durant, T. M., Oppenheimer, M. J., Lynch, P. R., Ascanio, G. and Webber, D.: Body Position in Relation to Venous Air Embolism: A Roentgeologic Study. Am. J. M. Sc. **227:** 509 (May), 1954.

Employing the biplane stereoscopic angiocardiograph, the authors were able to study the pathophysiology of venous air embolism. Identification of the structures involved was made by stainless steel markers placed about the pulmonary artery or by catheters placed in this structure via the great veins and by post mortem correlation. Air injected into the femoral vein in lethal doses ap

peared almost immediately in the heart and pulmonary artery. With the air embolus in the latter structure, systemic hypotension and marked respiratory arrhythmias were observed. In the left-side-down position the amount of air in the pulmonary artery progressively decreased in animals which recovered and was reciprocally related to the amount of air in the right atrium and ventricle. Here the air was trapped away from the right ventricular outflow tract so that blood could pass from the cavae into the pulmonary artery. In contrast, the supine position was very unfavorable since the obstructing air traps persisted in blocking right ventricular outflow. A dramatic film of a human case of venous air embolism is shown in which accidental aspiration of air occurred during angiocardiography.

SHUMAN

Muller, O. and Shillingford, J.: Tricuspid Incompetence. Brit. Heart J. **16:** 195, (Apr.), 1954.

Twenty-one individuals with tricuspid incompetence were studied clinically and by phonocardiography, phlebographic recordings and intracardiac catheterization. A differential diagnosis between organic tricuspid insufficiency due to tricuspid valvular disease and mere dilatation could not be made. Auricular fibrillation was present in 17 of the 21 cases. The venous pressure was above 8 centimeters in most. A systolic murmur at the lower end of the sternum increased by exercise or deep breathing and systolic pulsation in the internal jugular vein and pulsations of the liver were the characteristic physical findings.

SOLOFF

ROENTGENOLOGY

Takahashi, S. and Shinozaki, T.: Solidography of the Heart. Acta radiol. **41:** 435 (May), 1954.

The authors describe an improved technical method by which roentgenograms in various angles of rotation are used to reconstruct the size and shape of the heart. This is an adaptation of, and probably an improvement of, the method devised by Palmieri 24 years ago.

SCHWEDEL

Munk, J. and Lederer, K. T.: Inspiratory Widening of the Heart Shadow. A Fluoroscopic Sign in Acute Obstructive Laryngo-Tracheitis. Brit. J. Radiol. **27:** 294 (May), 1954.

The authors report inspiratory widening of the heart shadow during fluoroscopy in 20 cases of laryngo-tracheitis. This sign was also observed in upper respiratory obstruction and in bilateral obstructive emphysema. During expiration the heart shadow diminished in size.

The mechanism for the widening is assumed to be similar to the Valsalva test in which forced expiration takes place with the glottis closed (an artificially produced temporary obstruction at the glottis resulting in increased intrathoracic pressure and a diminished volume of the heart), and to the Müller's test in which a forced inspiration is taken with the glottis closed, resulting in increased heart size.

SCHWEDEL

SURGERY

Finkbeiner, J. A., Wroblewski, F. and LaDue, J. S.: The Effect of Chronic Auricular Fibrillation on the Operative Risk. Am. J. M. Sci. **227:** 535 (May), 1954.

In this report the preoperative status is correlated with the operative and postoperative course of 60 patients with chronic auricular fibrillation who were subjected to 76 major operations during a 6 year period. The operative mortality rate in these patients was 5 per cent. Cardiovascular complications occurred in 71 per cent of the 76 procedures; cardiopulmonary complications in 22 per cent; the operative and postoperative course was uncomplicated in only 23 per cent. The principal factors increasing the complication rate were inadequate digitalization, recent congestive heart failure, angina pectoris and a poor functional classification. In addition, complications were frequent in those with pulmonary emphysema, azotemia, generalized arteriosclerosis and obsesity. Fifteen of the patients with organic heart disease died of cardiovascular disease within 39 months of operation; of this group, 73 per cent of these had cardiac enlargement preoperatively. Stabilization of the cardiovascular, pulmonary, hepatic and renal systems preoperatively with emphasis upon complete digitalization is advocated in these patients. It is concluded that the patient with chronic auricular fibrillation is probably no greater an operative risk than the non-fibrillating patient with equal cardiac damage, providing the patient is adequately prepared preoperatively.

SHUMAN

Gerbode, F.: Surgical Treatment of Emergencies of the Heart and Vessels in the Thorax. J. A. M. A. **154:** 898 (Mar. 13), 1954.

Of all emergencies affecting the heart cardiac arrest requires the most urgent treatment. Prompt resuscitative measures should be instituted. One has but three to five minutes to act before permanent central nervous system changes, if not death, occur. Thoracotomy with massage, plus procaine amide or procaine into the right ventricular chamber and then the use of a defibrillating machine, are indicated when ventricular fibrillation is present. Cardiac standstill is treated by massage and calcium chloride solution (10 cc. of 10 per cent), or 0.5 cc. of a 1 in 1000 solution of epinephrine injected into the chamber of the right ventricle.

Contusion of the heart is treated as if infarction had occurred. Wounds of the vessels arising from the arch of the aorta may require median ster-

notomy, resection of the clavicle, or intercostal thoracotomy for control of hemorrhage. Both hemothorax and cardiac tamponade are best treated by repeated aspiration unless bleeding is continuous or massive (when thoracotomy is indicated).

Foreign bodies lodged in the region of the heart or great vessels should be removed due to the danger of pericarditis, erosion of the heart or vessels with hemorrhage, or aneurysm. There is no satisfactory treatment for dissecting aneurysms, but other aneurysms of the thoracic aorta or its great vessels may at times be successfully controlled by wiring, wrapping with reactive polyethylene film, or resection. When feasible, resection is preferred.

KITCHELL

Earle, B. K., and Zimmerman, H. A.: Surgical Repair of Intraventricular Septal Defects. J. A. M. A. **154:** 986 (Mar. 20), 1954.

This article describes a technic said to be simple, safe and adaptable to the closure of the majority of septal defects. After exposure of the heart and insertion of a purse-string suture in the anterior wall of the right ventricle an opening is made for the insertion of the index finger. The finger tip locates the defect in question. A large upholstery needle and number 1 nonabsorbable surgical suture is passed through the heart wall in the region of the pulmonary conus and the tip of the needle is directed by the index finger within the ventricular chamber. The needle engages the anterior and posterior lips of the septal defect and then goes through the ventricular wall at a lower level. The needle is removed and an instrument is passed into the ventricular chamber along with the index finger to catch the two ends of the suture and to bring them out. The ends are then tied and the knot is pushed into the chamber approximating the two lips of the defect. It seems that three to four sutures are necessary to close adequately defects that approach the size of the end of the finger. The myotomy incision is then closed by interrupted suture, and the purse-string suture is removed. Refrigeration of the patient adds to the safety of the operation.

KITCHELL

Maloney, J. V. Jr., and Blalock, A.: Problems in Cardiovascular Surgery. Ann. Int. Med. **40:** 1 (Jan.), 1954.

The authors present an excellent classification of congenital and acquired cardiovascular problems in which surgery may accomplish good or excellent results, in which surgical therapy may result in moderate improvement, and in which surgery is of doubtful value or suitable methods are not yet fully developed.

In the discussion of the surgical management of a wound of the heart, it is pointed out that open operations should be deferred until the effect of at least one pericardial aspiration has been determined. It is reported that the tubercle bacillus is the most frequent etiologic agent of constrictive pericarditis. The authors believe that the most important part of the procedure is the decortication of both the right and left ventricles. It is usually unnecessary to decorticate the auricles.

Other acquired cardiovascular problems amenable to surgery are discussed, such as aortic aneurysms, mitral stenosis, aortic stenosis, and the very challenging problem of insufficiency of the valves. The aspects of patent ductus arteriosus are presented and the operation is usually not performed until the child is two or more years of age. Ideally, operation should be performed in the first decade of life, before left ventricular hypertrophy and strain result from the excessive burden placed on the left ventricle by the systemic-to-pulmonary shunt. Coarctation of the aorta is best treated between the ages of 6 and 16 years. It is desirable to wait until the aorta has achieved most of its growth, when an anastomosis of maximal size can be expected. For stenosis of the pulmonary valve, the authors recommend division and dilatation of the valve by the right ventricular route. It has been their custom to perform this operation if the child is symptomatic or has progressive cardiac enlargement, or if cardiac catheterization shows severe right ventricular hypertension.

Finally, the authors point out that the surgical treatment of transposition of the great vessels, auricular and ventricular septal defects, and anomalies of the venous return is still in the developmental state.

DENNISON

Sellors, T. H., Bedford, D. E., and Somerville, W.: Valvotomy in the Treatment of Mitral Stenosis. Brit. Med. J. **2:** 1059 (Nov. 14), 1953.

In the opinion of the authors, the signs of a pliant diaphragmatic valve type of mitral stenosis (the variety most amenable to valvotomy) are a snapping apex beat, a snapping first sound (closing snap), and a loud opening snap of clicking quality. Additional evidence of severe mitral stenosis is provided by an intense diastolic murmur, a small sustained pulse and a small aorta by x-ray. The surgeon can feel the snapping movements of the mitral valve. They believe cardiac catheterization is not necessary and that an assessment of the state of the right ventricle by physical examination and x-rays is more valuable than an isolated determination of pulmonary artery pressure. Those cases who have recently become incapacitated by paroxysmal pulmonary edema are considered ideal. Mitral valvotomy was performed in 150 patients. The male to female ratio was 1 to 4. Atrial fibrillation was present in 41 per cent. Ages varied from 19 to 57 years. The immediate (within four days) mortality was 2.7 per cent. Four others died after an interval of one month or more. Of 111 cases who have been

followed long enough to permit assessment, good results were achieved in 74 per cent, and fair or poor results in the rest.

McKusick

Bellman, S. and Gothman, B.: Vascularization of One Year Old Homologous Aortic Grafts. Ann. Surg. **139:** 447 (Apr.), 1954.

A study was made of aortic and femoral grafts in dogs about one year after transplantation. In some instances the blood vessels were examined using microangiographic methods. The functional result was good in all grafts except one which was occluded by a thrombus. Microangiography revealed the presence of a rich blood supply both in the tissue surrounding the graft and in the adventitia laid down by the host. Blood vessel penetration from the adventitia into the media was demonstrated, as well as penetration into the ends of the graft from the scars which surrounded the suture lines.

Abramson

Hultgren, H. N., and Gerbode, F.: A Physiological Study of Experimental Left Atrium Inferior Vena Caval Anastomoses. Am. J. Physiol. **177:** 164 (Apr.), 1954.

Successful anastomoses of left atrium and inferior vena cava were made in four dogs. In the immediate postoperative period, the oxygen saturation was low but gradually recovered to about 80 per cent. This saturation fell during exercise. Approximately 53 per cent of the peripheral venous return entered the left atrium from the inferior vena cava. The superior vena cava contributed 37 per cent to the right atrium. Pulmonary arterial pressure was decreased.

Oppenheimer

Stead, W. W., Martin, F. E., and Middlebrook, J.: A Practical Physical Method for the Detection of Early Respiratory Acidosis During Thoracic Surgery. J. Thoracic Surg. **27:** 306 (Mar.), 1954.

The authors describe a simple method for the detection of early and slight rise in alveolar P_{CO_2}. This consists of a physical recording of endotracheal pressure during positive pressure. The basis for the use of the procedure is the fact that in the presence of an elevated blood P_{CO_2} the patient makes spontaneous respiratory efforts whenever there is a pause in the intermittent positive pressure administered by the anesthesiologist. When the blood P_{CO_2} is normal or low, these changes are not observed. By means of a recording of endotracheal pressure, the presence or absence of spontaneous respiratory efforts can be determined.

Abramson

Jarvis, F. J., and Kanar, E. A.: Physiologic Changes Following Obstruction of the Superior Vena Cava. J. Thoracic Surg. **27:** 213 (Mar.), 1954.

The physiologic changes produced by experimental occlusion of the superior vena cava at the cava-auricular juncture were studied in a series of dogs. It was found that temporary occlusion of two hours' duration was tolerated, the azygos system providing an immediate route for collateral shunt around the occlusion. The superior vena caval pressure rose rapidly to maintain a high plateau level, while that within the right auricle and the aorta fell only slightly. Permanent occlusion was tolerated by two dogs, while in four others this measure was fatal.

Abramson

Kunos, J., and Temesvari, A.: A New Surgical Method for Amelioration of Heart Failure. Ztschr. Kreislaufforsch. **43:** 196 (Mar.), 1954.

In four cases of valvular disease with chronic heart failure resistant to medical therapy, the external iliac and the epigastric veins were ligated bilaterally below Poupart's ligament. Immediately after the operation, the venous pressure in the upper extremities dropped and dyspnea disappeared. Subsequently increasing diuresis, regression of edema and a reduction in liver size were noted. With support by salt-poor diet and by mercurial diuretics, this improved condition remained stationary for a period of eight months.

Pick

Dickinson, P. H., and Walder, D. N.: Sympathectomy for Atherosclerosis: Preliminary Heating Test. Lancet **266:** 75 (Jan. 9), 1954.

The authors studied the effect of indirect vasodilatation on 28 patients with arteriosclerosis obliterans of the lower extremities and compared the results with the degree of clinical improvement in walking ability obtained with lumbar sympathectomy. They found that the heating test was of no prognostic value in forecasting the outcome of the operation. Sympathectomy was found to reduce intermittent claudication in less than half of the patients.

Abramson

Cooley, D. A. and DeBakey, M. E.: Surgical Treatment of Mitral and Aortic Stenoses. J. A. M. A. **155:** 235 (May 15), 1954.

One hundred ten patients undergoing mitral valvotomy showed a 9 per cent operative fatality rate. In 9 of the 10 deaths, the cause was found to be thrombosis and embolism. Seventy-four per cent of the survivors had good to excellent functional results. The results were more uniformly good in patients between the ages of 25 and 35 years, although striking improvement was reported in many of the severely incapacitated persons in the older age group. Five women in the series reported were pregnant. Commissurotomy was successfully performed with subsequent normal delivery. In pregnant women commissurotomies should preferably be per-

formed before the fifth month. In this series the recurrence of severe stenosis was not noted. Aortic stenosis presents a more complex therapeutic and surgical problem, however symptoms of reduced cardiac output have been relieved by valvotomy in properly selected cases. Aortic valvotomy considerably relieved the symptoms in two patients with congenital aortic stenosis. Of three patients with acquired aortic stenosis, two died and the other was improved. It is important to perform aortic valvotomy before the cardiac enlargement becomes pronounced and accompanying coronary insufficiency develops.

KITCHELL

Lurie, P. R. and Shumacker, H. B., Jr.: Mitral Commissurotomy in Childhood. Pediatrics **13**: 454 (May), 1954.

Three children, ages 12, 14, and 15, who had mitral stenosis were operated on and the results of mitral commissurotomy were good. The patients were asymptomatic but filled the generally accepted criteria for operability. Catheterization studies performed in two patients showed normal resting right ventricular diastolic pressures, elevation of the resting pulmonary artery pressure and pulmonary capillary pressure, and arterial hypoxemia during exercise. The authors feel that these studies show that children with mitral stenosis behave identically physiologically to adults with the lesion and that mitral commissurotomy can be beneficial at any age, however early, if the patient fits the generally accepted criteria for operation.

HARVEY

THROMBOEMBOLIC PHENOMENA

Peck, M. E.: Preliminary Observations on the Effect of Trypsin Administered Intravenously. J. A. M. A. **154**: 1260 (Apr. 10), 1954.

Recent investigations on the effect of the pancreatic enzyme trypsin, administered intravenously, may prove the opening wedge to a new line of approach toward the management of inflammatory processes. By January of 1953, over 300 cases of acute thrombophlebitis had been treated by trypsin intravenously and the results were uniformly dramatic. Encouraging results have also been obtained in small series of cases of simple retinal thrombosis, pulmonary infarction, certain chronic infectious diseases, carcinoma, and rheumatoid arthritis. In patients with thrombophlebitis, trypsin does not affect the basic anatomic defect that leads to the development of the process, but it does influence the acute inflammatory reaction, causing reduction in edema, healing of skin excoriation, and improvement in color of the extremities. Reactions to trypsin given intravenously fall into three categories. The immediate mild reaction is characterized by flushing of the face and a warm feeling. A latent reaction may begin about two hours after the start of an injection. These latent reactions consist of chilly sensations without temperature elevation or of true shaking chills with temperature elevation. Gradations of anorexia, nausea, abdominal cramps, vomiting, aching pain in the upper extremities may develop in such attacks. The secondary reactions may be thrombotic or embolic. Thrombotic responses occur after infusion in small veins and the reaction is similar to a chemical phlebitis except that it is more severe. Embolic secondary reactions have occurred in one patient and possibly a second. Both were in the terminal stage of malignant disease. More study needs to be done before this drug can be freely used in the treatment of patients and it may be that the dangers associated with trypsin will seriously limit the intravenous use of this enzyme.

KITCHELL

VASCULAR DISEASE

Edwards, E. A.: Varieties of Digital Ischemia and Their Management. New England J. Med. **250**: 709 (Apr. 29), 1954.

The mechanisms of digital ischemia and the wide variety of disorders with which it is associated are reviewed in detail. The close association of organic and spastic factors is emphasized and it is pointed out that almost any organic occlusion of the arteries may set off a reflex vasoconstriction. Agglutination of cellular elements may be suspected when there is distal cyanosis which is difficult to relieve by elevation or stroking. Fibrin is felt to play little role in such problems and it is not anticipated that anticoagulant therapy can prevent it. The signs of predominant vasospastic disease are inconstant ischemia, coldness without or out of proportion to major pulse loss, increased sweating of the hand or foot, thinning of the skin fold at the base of the nail, tightness and loss of cutaneous markings and skin folds of the digits or more of the limb, atrophy of the bony tufts of the terminal phalanges and painful, puckered ulcers at the tips of the digits. Many disorders which cause digital ischemia through vasospasm are described by the author. Others which occlude vessels organically but can cause secondary spasm are mentioned. For relief of vasospasm, the three general categories of treatment include physiologic maneuvers such as warmth and avoidance of tobacco, vasodilatation through non-surgical means, including dibenzyline which the author has found to be very useful, and sympathectomy, which is considered ideal so long as the disease is not a progressive organic disorder of the acral vessels. In the application of sympathectomy to the upper extremities the need for careful appraisal of the disorder and removal of an adequate length of sympathetic chain is emphasized.

ROSENBAUM

Chambers, W. R., Harper, B. F. and Simpson, J. R. Familial Incidence of Congenital Aneurysms o

Cerebral Arteries. J. A. M. A. **155:** 358 (May 22), 1954.

Although it has now been widely accepted that intracranial aneurysms are of a congenital nature, the possibility that there may be a familial factor in the occurrence of these aneurysms is a theory that has not yet been advanced to the knowledge of the authors. They present intracranial aneurysms proven in a father and son.

KITCHELL

Jepson, R. P.: The Effects of Vascular Occlusion and Local Cooling on Finger Skin Blood Flow. Clin. Sc. **13:** 259 (May), 1954.

Reactive hyperemia tests involving immersion in cold water and arterial occlusion by a sphygomanometer were performed on 65 persons. Heat flow was measured by a copper-tellurium disc. The vasodilator stimulus of arterial occlusion was often sufficient to offset the direct vasoconstrictor effect of cold, resulting in a rise in finger flow. The duration and amplitude of flow depended on several factors, the most important of which are the patient's age and the temperature of the water bath. The older age groups showed a smaller degree of reactive hyperemia, as did individuals with thin fingers. The test may fail to detect some patients with Raynaud's phenomenon, and may give false negative heat flow reactions in the older age groups. However it may be of value to exclude a marked local fault in the digital vessels in the younger age group.

ENSELBERG

OTHER SUBJECTS

Evans, B. M., Hughes Jones, N. C., Milne, M. D. and Steiner, S.: Electrolyte Excretion During Experimental Potassium Depletion in Man. Clin. Sc. **13:** 305 (May), 1954.

Potassium depletion was produced in normal subjects by the use of a low potassium diet and a cation exchange resin for a seven day period. Potassium excretion was increased over the next two days by several methods. The results demonstrated effective conservation of potassium in states of potassium deficiency despite such stimuli to excretion as hyperventilation, osmotic diuresis, carbonic anhydrase inhibitor (Diamox) and sodium bicarbonate. The results are compatible with the hypothesis that there is competition between potassium and hydrogen for exchange with sodium in the distal tubules, but this exchange may not occur when there is a diminution of available potassium and hydrogen. The observations also showed that carbonic anhydrase inhibitors are more effective during potassium depletion, and that therefore a high potassium intake should be avoided when these drugs are used clinically.

ENSELBERG

Groves, L. K. and Effler, D. B.: Primary Chylopericardium. New England J. Med. **250:** 520 (Mar. 25), 1954.

A case of primary chylopericardium occurring in a woman of 31 years is described. This is apparently the first such case to be reported. A cystic hygroma of the mediastinum (lymphangiomatous hamartoma) associated with an anatomic communication between the thoracic duct system and the pericardium was apparently responsible. The diagnosis was established by means of feeding the patient emulsified corn oil and milk in which Sudan III was dissolved and later recovering and extracting fat from the pericardial fluid stained with the dye. Apparent complete recovery followed ligation of the thoracic duct low in the chest and excision of the greater part of the mediastinal tumor mass.

ROSENBAUM

Carlson, L. A. and Olhagen, B.: The Electrophoretic Mobility of Chylomicrons in a Case of Essential Hyperlipemia. Scandinavian J. Clin. & Lab. Investigation **6:** 70 (No. 1), 1954.

This study is concerned with the electrophoretic migration of chylomicrons in a starch medium. The electrophoresis is carried out in a vertical tube filled with starch. When electrophoresis is completed, air pressure is applied to the cathodic end of the tube and the separated proteins are forced out by the buffer-flow through the anodic end of the tube and are collected in fractions of suitable volume. The study indicated that that is no appreciable absorption of chylomicrons in starch. As in previous experiments with free electrophoresis, the chylomicrons migrated as two distinct fractions, one associated with the α-globulin and the other with the β-globulin. This report is felt to demonstrate the superiority of the starch method to that of zone electrophoresis in paper, which gives the erroneous impression of a single immobile chylomicron fraction.

ROSENBAUM

Cort, J. H.: Cerebral Salt Wasting. Lancet **1:** 752, (Apr. 10), 1954.

A patient with right posterior thalamic tumor is described in whom extreme clinical dehydration was revealed by balance studies to be related to pronounced loss of sodium and potassium in the urine. Tests of adrenal and pituitary function were normal. These glands were essentially normal histologically at subsequent autopsy and replacement therapy with their hormones did not affect the syndrome. Anatomically the lesion was in a position to interrupt the descending fibres from the hypothalamus. The author suggests that this represented an "experiment of nature" comparable to that of Claude Bernard who found that a unilateral lesion in the reticular substance at the floor of the fourth ventricle produced a diuresis of chloride without a diuresis of glucose. Bernard reproduced the syndrome by renal denervation. The author echos the suggestion of Welt and other members of J. P. Peters' group that an interruption of hypothalamic-renal pathways

interferes with electrolyte reabsorption in the proximal tubule and results in an osmotic diuresis distally.

McKusick

White, W. E. and Reilly, W. A.: Chromatographic Changes in Plasma I^{131} During The Treatment of Graves' and Cardiac Diseases Correlated with Clinical Course. J. Lab. & Clin. Med. **43:** 553 (Apr.), 1954.

Nineteen patients with Graves' Disease and 4 patients with intractable angina pectoris were given radioiodine. Radio autography was carried out on filter paper chromatograms of plasma of these patients and the iodinated compounds of the plasma were measured. Correlation of the clinical effectiveness of the administered dose was made with the changing chromatographic plasma analysis. It was found that reduced intensity of the band of radioactive thyroxine within two to seven days forecasts euthyroidism; disappearance, hypothyroidism; and persistence, insufficient treatment.

Harvey

Laake, H.: Heart Disease and Pregnancy. A Follow-up Study of a Hospital Material. Acta med. Scandinav. **148:** 147 (Fasc. 2), 1954.

This report is based upon the review of the experience of 116 women with organic heart disease who underwent one or more pregnancies. Fifty-six nulliparae with organic heart disease treated at the same hospital during the same period served as controls. Two-thirds of the observed group had one or two pregnancies but a few women had many infants and 10 had six or more. It was concluded that the number of patients with heart disease who have serious trouble during their pregnancies is small. It was found that the majority of patients who did develop cardiac decompensation developed it during the puerperium. No connection could be demonstrated between the incidence of congestive failure and the number of births. There was no correlation between the location of the valvular involvement and the incidence of heart failure. It was observed that signs of heart failure following confinement tended to increase in frequency as the interval between the first attack of rheumatic fever and confinement lengthened. When the number of births was correlated with the years between the last pregnancy and the appearance of heart failure, there was no correlation between the number of pregnancies and the incidence of heart failure. There seemed to be no effect upon the prognosis whether there had been several attacks or only one of rheumatic fever. So far as longevity and age at the time of onset of congestive failure, there seemed to be no statistically demonstrable difference between the patients who had been confined and the nulliparae. There were seven cases of congenital heart disease, largely of the acyanotic type. They did not appear to be influenced unfavorably by the pregnancies. The author concludes that the heart's functional capacity to respond to work is the most reliable guide to selection of cases, even though we do not possess exact methods for determining cardiac reserves.

Rosenbaum

Howarth, S.: Atrial Waves on Arterial Pressure Records in Normal Rhythm, Heart Block, and Auricular Flutter. Brit. Heart J. **16:** 171 (Apr.), 1954.

Waves produced by atrial contraction are seen in records taken from the brachial artery of individuals with sinus rhythm, heart block, and auricular flutter. When the waves are isolated, a triphasic wave consisting of a positive negative and positive phase are seen; when the waves are not isolated the atrial wave is seen as a monophasic positive wave. The mechanism for the production of this wave is speculative.

Soloff

Miller, G., McCoord, A. B., Joos, H. A. and Clausen, S. W.: Studies of Serum Electrolyte Changes During Exchange Transfusion. Pediatrics **13:** 412 (May), 1954.

Eight new born infants with erythroblastosis fetalis were treated by exchange transfusions. The concentration of potassium in each donor plasma was measured. Serum potassium levels were determined in the infants during and after the transfusion. Donor blood stored over 4 days had high serum potassium levels (7.2 mEq. per L to 18.2 mEq. per L). Four of the infants were transfused with this type of blood which had been stored for 9, 16, 17, and 21 days respectively. Two infants in this group developed high serum potassium levels but these infants exhibited neither ill effects from the high levels nor electrocardiographic changes. No significant changes in potassium levels were observed in the other 6 infants of whom two were subjected to transfusion with blood of high serum potassium levels (7.2 mEq. per L and 12.3 mEq. per L respectively), and 4 were subjected to transfusion with blood of normal serum potassium levels.

Harvey

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Der Herzanfall, Differentialdiagnose und Therapie. Herausgegeben von der Vereinigung der Bad Nauheimer Arzte (Nauheimer Fortbildungs Lehrgänge, Band 19.) Darmstadt, Verlag von Dr. Dietrich Steinkopff, 1954. 130 pages, 38 figures. Price—DM 13.– Available through: Intercontinental Medical Book Corp. 381 4th Avenue, New York.

Der Herzkatheterismus beiangeborenen und erworbenen Herzfehlern. *Prof. Dr. Otto Bayer, Dr. Franz Loogen, and Dr. H. Helmuth Wolter.* Foreword by Prof. Dr. Erich Boden. Stuttgart, Georg Thieme Verlag, 1954. 191 pages, 131 figures. $8.60 U. S. agent: Intercontinental Medical Book Corp.

Hypertension and Nephritis. *Arthur M. Fishberg, M.D.*, Fifth Edition. Philadelphia, Lea & Febiger, 1954. 986 pages, 49 figures. $12.50.

Greater Works. Stories and Articles on the Cure of the Sick and the Care of the Unfortunate. *Compiled and Arranged with Commentary by Leona Meyer Wegener.* New York, Exposition Press, 1954. 246 pages. $3.50.

Il Fegato dei Cardiaci. *A. Poppi, G. Labò, G. Lenzi,* Preface by Prof. G. Sotfiu. Bologna, L. Capelli, Editore, 1954. 291 pages, 101 figures, 122 tables. No price.

Atlas Postmortaler Angiogramme. *Dr. J. Schoenmackers, und Dr. H. Victen.* Stuttgart, George Thieme Verlag, 1954. 203 pages, 145 figures. $13.55. U. S. agent: Intercontinental Medical Book Corp., 381 4th Ave., N. Y.

El Instituto Nacionale de Cardiologia a los diez años de su fundacion. *Dr. Ignacio Chavez.* Printed by Instituto N. de Cardiologia, Mexico, 1954. 47 pages.

Heart Disease and Industry with particular reference to Workmen's Compensation cases. *Meyer Texon, M.D.* Forewords by Samuel A. Levine, M.D., and Hubert Winston Smith, LLB., M.D. New York, Grune & Stratton, 1954. 324 pages. $7.50.

Regulationsprüfung des Kreislaufs. Funktionelle Differentialdiagnose von Herz-und Gefäbstörungen. Volume II. *Fritz Schellong M.D. und Bernhard Luderitz, M.D.* Darmstadt, Verlag von Dr. Dietrich Steinkopff, 1954. 150 pages. DM 22.–

Peripheral Circulation in Man. A Ciba Foundation Symposium. *Editors for the Ciba Foundation: G. E. W. Wolstenholme, and Jessie S. Freeman assisted by Joan Etherington.* Boston, Little, Brown, 1954. 219 pages, 72 figures. $6.00.

The Bacterial Factor in Traumatic Shock. *Jacob Fine, M.D.*, Springfield, Charles C Thomas, Publishers, 1954. American Lectures Series in Circulation, #219. 82 pages, 3 figures, 9 tables. $2.75.

A Primer of Pulmonary Function. *Harold Guyton Trimble, M.D., and James Kiernan, M.D.* Printed through the cooperation of California Tuberculosis and Health Association. 22 pages, 1 table, 1 figure.

Myokardstoffwechsel und Herztherapie. *Fritz Pendl. M.D.*, Stuttgart, Georg Thieme Verlag, 1954. 248 pages, 26 figures, 7 tables. DM 29.70 ($4.10). U. S. agent: Intercontinental Medical Book Corp.

The Doctor Writes, An Anthology of the Unusual in Current Medical Literature. Edited by S. O. Waife, M.D. New York, Grune & Stratton, 1954. 175 pages, 8 figures. $3.75.

Why We Became Doctors. *Noah D. Fabricant, M.D.* New York, Grune & Stratton, 1954. 182 pages. $3.75.

Coronary Heart Disease in Young Adults. A Multidisplinary Study. *Menard Gertler, M.D., and Paul D. White, M.D. With the Aid, Advice and Editorial Assistance of E. F. Bland, M.D., J. Fertig, Ph.D., S. M. Garn, Ph.D., J. Lerman, M.D., S. A. Levine, M.D., H. B. Sprague, M.D., and N. C. Turner, M.Sc.* Published for the Commonwealth Fund by Harvard University Press, Cambridge, Mass., 1954. 218 pages, 25 figures, 61 tables. $5.00.

Medical Uses of Cortisone Including Hydrocortisone and Corticotropin. *Francis D. W. Lukens,* New York & Toronto, The Blakiston Company, Inc., 1954. 534 pages, 52 figures, 35 tables. $7.50.

Clinical Pathologic Conferences of Cook County Hospital. Volume I. Cardiovascular-Renal Problems. *Edited by Hans Popper, M.D., Ph.D., and Daniel S. Kushner, M.D.* New York & Toronto, The Blakiston Company, Inc., 1954. 325 pages, 70 figures. $5.00.

Emergency Treatment and Management. *Thomas Flint, Jr., M.D.* Philadelphia, W. B. Saunders, Company, 1954. 303 pages. $5.75.

The Digital Circulation. *Milton Mendlowitz, M.D.* New York, Grune & Stratton, 1954. 182 pages, 31 tables, 60 figures. $6.75.

Of Publishing Scientific Papers. *George E. Burch, M.D.* New York, Grune & Stratton, 20 pages, 18 figures. $2.75.

Ciba Foundation Symposium on Hypertension, Humoral and Neurogenic Factors. Editors for the Ciba Foundation: *G. E. W. Wolstenholme, M.B.,*

and Margaret P. Cameron, M.A. Assisted by Joan Etherington. Boston, Little, Brown and Company, 1954. 294 pages, 73 illustrations. $6.75.

L'Année Cardiologique Internationale. *Direction of Professeur Camille Lian. L'Expansion Scientifique Francaise*, Paris, 1954. 1 volume. 382 pages, 3,000 frs.

Einführung in die Psychosomatische Medizin. *Prof. Dr. Medard Boss.* Bern and Stuttgart, Verlag Hans Huber, 1954. 224 pages, 21 figures. DM 19.80. U. S. agent: Intercontinental Medical Book Corp.

Das Postthrombotische Syndrom. Pathogense, Diagnostik, Behandung und Verhutung der Folgezustände nach akuter Beinvenenthrombose. *Th. Halse, M.D.* Darmstadt, Verlag Von Dr. Dietrich Steinkopff, 1954. 114 pages, 34 figures. DM 20.

Cerebrovascular Disease. *James Peter Murphy, M.D.* Chicago, The Year Book Publishers, Inc., 1954. 408 pages, 128 figures. $12.00.

Textbook of Pediatrics. *Edited by Waldo E. Nelson, M.D.* Sixth Edition. Philadelphia, W. B. Saunders Company, 1954. 1581 pages, 440 figures, 127 tables.

Fundamentals of Internal Medicine. *Edited by Wallace M. Yater, M.D.* Fourth Edition. New York, Appleton-Century, 1954. 1276 pages, 140 figures, 62 tables, 1 color plate. $13.50.

Symposium on the Cardiac in Industry. Held Under the Auspices of Golden Clinic, Memorial General Hospital Association, Elkins, West Virginia. 1953. 135 pages.

Myocardial Infarction. Its Clinical Manifestations and Treatment with Anticoagulants. A Study of 1031 Cases. *Irving S. Wright, M.D., Charles D. Marple, M.D., and Dorothy Fahs Beck, Ph.D.* Published for the American Heart Association by Grune & Stratton, New York, 1954. 656 pages, 180 figures, 171 tables with 12 figures and 94 tables in Appendices, $8.50.

Principles of Internal Medicine. Second Edition. *Editors: T. R. Harrison, Raymond D. Adams, Paul B. Beeson, William H. Resnik, George W. Thorn, and M. M. Wintrobe.* The Blakiston Company, New York and Toronto, 1954. 1791 pages, 206 figures, 149 tables with 5 color plates. Student Edition 1-Volume $16.00; Profession 2-Volumes Edition—$21.00.

Atlas of Congenital Cardiac Disease. *Maude E. Abbott, B.A., M.D., F.R.C.P.* (Canada). Originally published by the American Heart Association, New York 1936. Reprint published by the American Heart Association, 1954. 62 pages, 25 plates, 1 table. $5.00.

Herzkrankheiten im Säuglingsalter. *Priv.-Doz. Dr. Ettore Rossi.* Foreword by Prof. Dr. Guido Fanconi. Stuttgart, Georg Thieme Verlag, 1954. 373 pages, 198 figures with 369 plates and 14 tables. $15.45. U. S. agent: Intercontinental Medical Book Corp.

La Valvola Mitrale. Aspetti anatomici, fisiologici, clinicic e chirurgici. Michele A. Chiechi and Charles P. Bailey. Il Pensiero Scientifico Editore, Rome, Italy, 1954. 561 pages, 158 figures, 12 tables. 5000 Lire.

The Auxiliary Heart. *William Walter Wasson, M.D.* Springfield, Charles C Thomas, 1954. 184 pages, 72 figures. $10.50.

Urology. *Meredith Campbell, M.S., M.D., F.A.C.S.* With the Collaboration of 51 Contributing Authorities. Philadelphia, W. B. Saunders Company, 1954. Three volumes. 2356 pages, 1148 figures. $60.00.

Clinical Electrocardiography. *David Scherf, M.D., F.A.C.P., and Linn J. Boyd, Jr., M.D., F.A.C.P.* New York, Grune & Stratton, 1953. Fourth Revised Edition. 490 pages, 292 figures. $7.50.

Angina Pectoris. Entstehung, Erkennung, Beurteiling und Behandlung der Herzschmerzanfälle. Prof. Dr. W. H. Hauss. Foreword by Prof. Dr. Ferdinand Hoff. Stuttgart, Georg Thieme Verlag, 1954. 394 pages, 127 figures (187 plates with 2 color plates), 23 tables. $14.15. U. S. agent: Intercontinental Medical Book Corp.

Angiopathia Diabetica. Konservative Behandlung des Zuckerbrandes. *Prof. Dr. M. Bürger.* Stuttgart, Georg Thieme Verlag, 1954. 190 pages, 81 figures including 6 color plates, 64 tables. Price, $16.40. U. S. agent: Intercontinental Medical Book Corp.

BOOK REVIEWS

Atlas of Congenital Cardiac Disease. *Maude E. Abbott, M.D.* New York, American Heart Association, Inc., 1954. 62 pages, 25 plates. $5.00. (Exact facsimile of the original Atlas which was published by the Association in 1936. Reprinted in limited edition of 1500 copies, each numbered.)

This classic monograph, first published in 1936, has long been out of print. While no library on cardiology should be without this volume, the decision of the American Heart Association to reprint it was mainly in response to numerous requests from students, investigators, clinicians, surgeons and bibliophiles who earnestly desire copies of their own. This reprint is, then, intended to satisfy primarily an emotional and intellectual appeal, though it is hoped that it will also fulfill a practical need.

The history of man's knowledge of the development of the heart and of the occurrence of congenital cardiac defects can be traced to Aristotle (4th century, B.C.), but it was Maude Abbott (1869–1940) who bridged the gap between the old, unsystematic and purely descriptive knowledge of congenital cardiac anomalies and the modern era of precise diagnosis and dramatic surgical correction of these defects. In fact, it was largely her systematic study and classification of these defects which opened the way for the astounding practical developments of the past two decades.

Maude Abbott was a prolific contributor to our knowledge of congenital anomalies of the heart and great vessels. Her enthusiastic study of the subject and her teachings not only contributed important knowledge but served to provide the necessary impetus for subsequent developments. Her first major report appeared in 1908 as a section of volume 4 in Osler and McCrae's "Modern Medicine" and was based on 412 cases of congenital heart defects gathered from her own collection of material and from the world medical literature. A steady flow of articles appeared through the years. Then, in 1936, came her "Atlas", a critical analysis of 1000 cases of congenital cardiac anomalies.

Reprinting of The Atlas was undertaken with the encouragement of Doctor William W. Francis of the Osler Library, McGill University, and with the permission of the Executors of Doctor Abbott's Estate. The American Heart Association may take pride in making the book available once again.

CHARLES MARPLE, M. D.

Myocardial Infarction. Its Clinical Manifestations and Treatment with Anticoagulants. A Study of 1,031 Cases. *Irving S. Wright, M.D., Charles D. Marple, M.D., and Dorothy Fahs Beck, Ph.D.* Published for the American Heart Association by Grune & Stratton, Inc., New York, 1954. 656 pages, 180 figures, 171 tables with 12 figures and 94 tables in Appendices. $8.50.

Ever since the first use of anticoagulants in the treatment of acute myocardial infarction there has been need for an extensive study relative to the benefit or lack of benefit of use of anticoagulants in treatment of this condition. Because administration of anticoagulants may not have a striking effect on the course in a single case or on the outcome in several cases of acute myocardial infarction, a study of many cases with adequate control cases which did not receive anticoagulants has been needed.

This report of a project of the Committee on Anticoagulants of the American Heart Association, is based on study of 1,031 cases of acute myocardial infarction; 16 hospitals with staffs of reliable stature participated in the study. Included in the book are 180 illustrations and 171 tables, 171 pages of appendices including 91 tables, and 267 references. Statistical analysis, accounting for the appearance of Dorothy Fahs Beck, Ph.D., as an author, is extensive; explanation of the method is given in appendix C. The relationship of age, diabetes, hypertension, obesity, values for cholesterol in the blood, and sex to acute myocardial infarction as well as of the course and management of the disease is considered extensively. Some may complain that the report is too extensive, but it is probable that more would have complained had the report been briefer and less detailed.

Five hundred and eighty-nine patients with acute myocardial infarction were treated with anticoagulants and 442 patients were not treated with anticoagulants. Only patients who were under hospital supervision and who survived the first 24 hours have been considered. The decision to administer anticoagulants or to withhold such treatment was based on the day of the month on which patients were admitted to hospitals; those admitted on days which were "odd" (for example, July 13) received anticoagulants and those admitted to hospitals on "even" days (for example, July 14) did not receive anticoagulants. The death rate in the control group was 23.4 per cent and in the treated group was 16.0 per cent. The reduction in death rate was almost wholly due to reduction in the number of deaths subsequent to thromboembolic complications; "42 per cent of the control group deaths but only 23 per cent of the treated group deaths were found to have been preceded by clinically diagnosed thromboembolic complication."

The authors concluded that in order to achieve the greatest benefit from Dicumarol and related substances, the blood should have a prothrombin activity of 23 per cent or slightly less. The number of bleeding episodes for each 1,000 days of therapy varied from 1.5 (prothrombin activity, 40 to 48 per cent) to 20.6 (prothrombin activity less than 6.3 per cent). Sixty-three per cent of the patients who

died and who had not had anticoagulants had mural thrombi but only 32 per cent of the patients who died who had received anticoagulants had mural thrombi of the heart. Necropsy disclosed 125 thromboembolic complications for each 100 deaths in the untreated group and 45 thromboembolic complications for each 100 deaths in the treated group. The consequences of nonfatal hemorrhage associated with the use of anticoagulants were mostly minor, transient, easily controlled and left no permanent sequelae. Necropsy (without microscopy) indicated extracardiac hemorrhage in 17 per cent of the untreated cases and 20 per cent of the treated cases. Rupture of the heart (necropsy study) was about twice as common in the treated group as in the untreated group (about 19 per cent and 8 per cent respectively).

The authors recognized the increased danger from hemorrhage and cardiac rupture when anticoagulants are used but pointed out that in their studies this disadvantage is compensated for about five times by reduction in thromboembolic complications. They recommended continuation of anticoagulant treatment for three to four weeks in the absence of contraindications. They stated that when physicians have extensive knowledge as well as wholly reliable laboratory reports on prothrombin activity, maximal protection is afforded against thromboembolic complications.

This report of a splendidly planned and well-executed study project has great value because of the close similarity in the nature of the episodes of illness of patients in the group which did not receive anticoagulants and in the group which did receive anticoagulants. Also the medical histories of patients in the two groups were similar and patients in both groups received about the same treatment except for the use of anticoagulants. The authors expressed the view that results would have been better had treatment with anticoagulants been better, for "about 59 per cent of the total period of observation for the treated group came within the period of potentially effective anticoagulant therapy with Dicumarol, namely, the period between the fourth day of anticoagulants and the day of the last dose. Even within this period of potential protection, doses were commonly inadequate to maintain patients within the optimum therapeutic range."

Good summaries are provided at the end of each chapter, a virtue particularly helpful to the physician who is cowed by statistical considerations and annoyed by details.

The observations mentioned in this review represent only a part of the record of the results of a model co-operative study of clinical investigation. The report considered in its entirety will undoubtedly serve as a reference source for years to come, for it records truth as far as a truth could be ascertained under the circumstances of the study and affords sharp contrast to opinion and prejudice. It should be most useful to physicians interested in anticoagulants and cardiovascular diseases but it should be available in every medical library and read by every physician who is confronted with questions relative to acute myocardial infarction, particularly the question: "Should I or should I not use anticoagulants?" The volume is most highly recommended.

EDGAR V. ALLEN, M.D.

Electrocardiographe Clinique. *J. Lenègre, G. Carouse and H. Chevalier.* Preface by Doctor Ch. Laubry. 810 pages. 341 illustrative electrocardiograms and 53 illustrative drawings. Paris, Masson et Cie., 1954. 7.600 fr.

The well known French clinician, Jean Lenègre and two of his associates have here assembled their experience with the electrocardiogram. The book brings the reader a compendium of Doctor Lenègre's electrocardiographic interests, drawn from the fruitful background of the extensive and modern clinical, pathologic and hemodynamic knowledge of the authors. In offering this monograph however, they state at once that they have no wish to encompass all of electrocardiography, but rather set themselves the task of making this science understood and particularly of providing a means by which physicians will interpret tracings correctly.

The text is divided into six parts. The first two are devoted to the technic and electrophysiologic basis of the electrocardiogram. These are the least satisfactory parts of the book. The third section sets forth the characteristics of the normal tracing, including those of infants and children, the esophageal and endocavitary potentials and vectorcardiograms. Although on minor points there could be disagreement (e.g. the authors advise using the shortest measurable P-R interval) this section is clear and highly informative. One must particularly compliment the authors on the excellence of the explanatory drawings presented in this section, many of them borrowed from well known original articles. An extensive fourth section reviews the principal abnormal patterns, covering the hypertrophies, bundle branch block and coronary lesions. This section is well conceived and since the authors present a thorough digest of the current literature, with few omissions, there is little room for disagreement. However, since this is a book for practioners, one would have wished that in discussing the temporal relationship between myocardial infarcts and their electrocardiographic expression the authors had mentioned the long delay possible between the occurrence of the infarct and its electrocardiographic signs, with warning to the reader that minor electrocardiographic signs may occur in the presence of the necrotic lesion.

In part five, the authors discuss the electrocardiographic findings in certain clinical states. The examples selected as subject matter are primarily those of special interest to the authors and unfortunately do not represent the complete and thorough review which would be necessary in a volume in

tended for general use. The choice of illustrations in the congenital heart chapter is entirely limited by their origin, namely the authors' own supply of tracings or those of close colleagues. This renders the section exceedingly limited and actually misleading in its narrowness. This is especially true of examples given of pure pulmonic stenosis and Ebstein's Anomaly. It is also regrettable that the chapter on cardiac drug effects discusses only digitalis and quinidine.

The final section on arrhythmias is the least informative. The longest part is given over to a detailed discussion of extrasystoles and the section including the major arrhythmias is by comparison short and inadequate. The interpretation of some of the examples of arrhythmias is open to discussion.

A word concerning the illustrations must be added since they comprise the largest section of the volume and are drawn almost exclusively from the authors' own files. They all contain a clinical summary, an x-ray description of x-ray findings, an autopsy comment where available, and an interpretation of the tracing. The clinical and autopsy comments are sometimes too superficial to be of value and the x-ray description is often too scant and not informative enough. The background markings of the tracings themselves unfortunately are often invisible, making any temporal or amplitude mensurations impossible for the reader.

In summary, this volume is sometimes overlong and repetitious, but it will prove to be an excellent reference volume since it summarizes the modern literature in a commendable fashion and gives the authors' own experience. However, as Doctor Laubry indicates in his preface, this book belongs rather on the shelf of the consultant and would be less useful to the student or general practitioner.

M. Irené Ferrer

Traité des Cardiopathies Congénitales. *Under the direction of E. Donzelot and F. D'Allaines; R. Heim de Balsac, C. Metianu, M. Durand, Ch. Dubost, J. le Brigand, M. Allary, N. du Bouchet, A.-M. Emam-Zade, J.-E. Escalle, B. Latscha, and N. Oeconomos.* VIII. + 1118 pages; 1155 illustrations. Paris, Masson et Cie, 1954. 14,650 fr.

This volume, written by some of the most competent cardiologists in the world, is probably the most comprehensive and authoritative book on congenital heart disease in existence at the present time. The chief co-authors are Doctors R. Heim de Balsac and C. Metianu, assisted by numerous specialists. The work is based on more than 1200 cases of congenital heart disease studied in the Medical Department (Professor E. Donzelot) and the Surgical Department (Professor F. D'Allaines) of the Hospital Broussais of Paris.

The book not only summarizes the studies published in "Archives des maladies du coeur et des vaisseaux" during the recent years, but it also contains numerous cases not previously published. The embryology, clinical diagnosis by the most advanced methods such as cardiac catheterization, angiocardiography, and radiokymography, as well as the medical and surgical treatment, are outlined in thorough but easy-to-read form, illustrated by numerous excellent radiograms, electrocardiograms, intracardiac pressure pulses, and anatomical specimens. At the end of the book the diagnosis and prognosis of the different types of congenital heart disease have been summarized in the form of tables. Each chapter has an extensive, up-to-date bibliography, while books and monographs on congenital heart disease are listed at the end of the book. While the results of the most modern laboratory technics are incorporated, the authors stress also the simpler diagnostic procedures available to the practicing physician, such as the intravenous ether test, developed by the authors of the book, for the diagnosis of a right-to-left shunt. Because of the large size of the book an inferior grade of paper had to be used, but this does not interfere with the clarity of the reproductions.

The exact diagnosis of the various forms of congenital heart disease has become increasingly important since the advent of successful operative technics for the surgical treatment of many anomalies. Such a diagnosis is now expected not only of the cardiologist but in many cases even of the medical practitioner. The reviewer does not hesitate to recommend the book under consideration to anyone concerned with the handling of patients with congenital anomalies of the heart; the clarity of the text makes only a superficial knowledge of the French language sufficient to understand the book adequately.

Eugene Lepeschkin

Spatial Vectorcardiography, *George E. Burch, J. A. Abildskov and J. A. Cronvich.* 173 pages, 121 illustrations, 19 tables. Philadelphia, Lea & Febiger, 1953. $5.00.

This interesting monograph is based on an exhibit presented at a meeting of the American Medical Association in June 1952. It summarizes studies made by the authors at Tulane University School of Medicine and the Charity Hospital at New Orleans. It briefly describes the concepts of vectorcardiography, some of the more common methods of electrode placement, and a summary of the authors' observations of frontal and sagittal plane vectorcardiograms in normal cases and in abnormal conditions, such as left ventricular hypertrophy, bundle branch block and myocardial infarction. Unfortunately, there is no description of normal or abnormal patterns in the horizontal plane vectorcardiogram and there is no index. It is the hope of this reviewer that these features will be added to the next edition. The monograph will be of interest to all physicians interested in the problems of vectorcardiography.

Emanuel Goldberger

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

SCHEDULE OF 1955 AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

All those who wish to present papers to the 28th Annual Scientific Sessions of the Association are urged to submit abstracts (not over 300 words) before July 1, 1955. The Scientific Session will be held during the first three days of the AHA Annual Meeting at the Jung Hotel in New Orleans, October 22–26. Abstracts should be submitted to the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N. Y.

The Scientific Session will be divided into general meetings and specialized sessions sponsored by sections of the Scientific Council, including the Section on Cardiovascular Surgery, the Section on Clinical Cardiology, the Section on Basic Science, the Section on Circulation and the Council for High Blood Pressure Research. Programs sponsored by the Council on Community Service and Education and the Council on Rheumatic Fever and Congenital Heart Disease will be held on October 23 and 24.

The Association's Annual dinner will be held on Monday evening, October 24. Section dinners are planned on October 22 and 23. Also included in the plans is a post-meeting tour of Mexico.

The Assembly, highest governing body of the Association, will gather on October 26 following Assembly panel meetings on October 25. An Assembly luncheon will also be held on October 25.

NEW HEART MODEL DESIGNED TO ASSIST IN TEACHING

A new functional heart model for use in medical and nursing schools and in graduate courses for physicians is now available from the American Heart Association. The model cast in latex and lucite was developed for the Association by Leon Schlossberg, medical illustrator at Johns Hopkins Hospital.

A feature of the life-size model of the great vessels and the normal heart in diastole is the clear lucite anterior surface on a hinged door. This transparent surface permits close examination of the valves, atria and ventricles. Important structural landmarks, both internal and external, are clearly numbered and the handy reference key is mounted on the plastic base.

Lucite pegs projecting from the base into the descending aorta and the inferior vena cava hold the model in its anatomical position and allow it to be readily removed for examination and demonstration.

The heart model can be ordered directly from the American Heart Association, 44 East 23 Street, New York 10, N. Y. or from affiliated Heart Associations. The cost is $50 postpaid. Two weeks should be allowed for delivery.

"SPEAKING FROM THE HEART"

"Speaking from the Heart," the 1954 Annual Report of the Association, is now available upon request.

This report reviews the joint research support program conducted during the year by the Association and its affiliates. It reveals that 50.9 per cent of all national office appropriations made for the 1953–54 fiscal year went for research support. This amounted to close to one million dollars. An additional sum of more than $1,800,000 was appropriated by affiliated Heart Associations to aid investigations in the cardiovascular field. Many of the gains in medical knowledge made through these expenditures are summarized.

In a section entitled "Speaking to Doctors," the annual report describes some highlights of the Association's medical education program including the 1954 scientific sessions, held in conjunction with the Second World Congress of Cardiology, and the inaugural scientific meeting of the Section on Clinical Cardiology.

Other medical educational features reviewed

include periodicals, manuals, extensive reports of studies on various aspects of cardiological investigation, meetings proceedings recording the results of scientific research, films and heart models.

CLEVELAND HEART SOCIETY SPONSORS CARDIAC RESUSCITATION COURSES

A series of two-day postgraduate courses on the "Prevention and Management of Cardiac Arrest" has been inaugurated by the Cleveland Area Heart Society. The courses, under the direction of Claude S. Beck, M.D., are being conducted at the Western Reserve School of Medicine in Cleveland.

The courses, each limited to 20 students, are being held every month with physicians, registered nurses and anesthetists eligible to attend.

Robert M. Hosler, M.D. is Associate Director of the program and participants include Drs. Herman K. Hellerstein and David S. Leighninger. Course dates for the remainder of the year are April 22–23, May 20–21, June 17–18, September 23–24, October 21–22, November 18–19 and December 16–17.

Tuition fees are $20 for Cleveland area residents and $40 for others. There is no charge for resident physicians and interns. Requests for information and applications should be addressed to the Registrar, Post Graduate Course in Resuscitation, Cleveland Area Heart Society, 2073 East Ninth Street, Cleveland 10, Ohio.

GEORGIA ESTABLISHES AWARD FOR YOUNGER PHYSICIANS

An award for young physicians has been established by the Georgia Heart Association for the best paper (up to 7,000 words) on any subject in the cardiovascular field. Among those eligible to submit entries are interns, house officers and fellows in Georgia hospitals; Georgia physicians who have been in practice or under five years; and Georgia citizens in the armed forces who have practiced medicine or less than five years.

Papers must be submitted by June 1 to be eligible for this year's award, in the amount of $100, which will be made at the annual meeting of the Georgia Heart Association. Details may be obtained from the Chairman, Awards Committee, Georgia Heart Association, 318 Western Union Building, Atlanta 3, Ga.

SOUTH CENTRAL ALASKA BECOMES 56th AFFILIATE

The South Central Alaska Heart Association has become the 56th direct affiliate of the A.H.A. Officers of the new Association include Robert B. Wilkins, M.D. President; Robert H. Romig, Vice President; Mrs. Ruth McLaughlin, Secretary; and Ben Crawford, Treasurer. Mailing address of the Alaskan affiliate is P.O. Box 1460, Anchorage, Alaska.

BLAKESLEE AWARD DEADLINE POSTPONED UNTIL MAY 1

The deadline date for submission of entries for the third annual Howard W. Blakeslee Awards of the American Heart Association has been extended until May 1. Materials in the fields of press, magazines, books, radio, television and films which have been published, issued or produced between January 1, 1954 and March 1, 1955 will be eligible for the 1955 awards.

MAY 31 ABSTRACT DEADLINE SET FOR ARTERIOSCLEROSIS MEETING

May 31 has been set as the deadline for submission of abstracts for the 1955 annual meeting of the American Society for the Study of Arteriosclerosis. The meeting is to be held at the Sheraton Hotel, Chicago, November 6 and 7. Factual abstracts (original and four copies) should be sent to Charles F. Wilkinson, Jr., M.D., Program Chairman, 550 First Avenue, New York 16, N. Y.

MEETINGS CALENDAR

April 10–16: American Society of Experimental Pathology, San Francisco. Cyrus C. Erickson, 874 Union Avenue, Memphis 3.

April 10–16: American Society for Pharmacology and Experimental Therapeutics, San Francisco. Carl C. Pfeiffer, 1853 W. Polk Street, Chicago 12.

April 23–29: Industrial Medical Association, Buffalo, New York. H. Glenn Gardiner, Inland Steel Co., East Chicago, Indiana.

April 24–29: Inter-American Congress of Radiology, Shoreham Hotel, Washington, D. C., Dr. Eugene P. Pendergrass, 3400 Spruce St., Philadelphia 4.

April 27–29: American Surgical Association, Philadelphia. R. Kennedy Gilchrist, 59 East Madison Street, Chicago 3.

May 1: American Federation for Clinical Research, Steel Pier Theatre, Atlantic City. Dr. William H. Beierwaltes, University Hospital, Ann Arbor, Michigan.

May 2: American Society for Clinical Investigation, Atlantic City. J. D. Meyers, 622 West 168th Street, New York 32.

May 3: Association of American Physicians, Atlantic City. W. Barry Wood, Jr., 600 S. Kingshighway Blvd., St. Louis.

May 8–13: Society of American Bacteriologists, New York. J. H. Bailey, Sterling-Winthrop Research Institute, Rensselaer, New York.

May 23–27: National Tuberculosis Association, Milwaukee. Mrs. Morrell DeReign, 1790 Broadway, New York 19.

June 2: The Endocrine Society, Atlantic City. H. H. Turner, 1200 N. Walker Street, Oklahoma City.

June 3–4: American Rheumatism Association, Hotel Dennis, Atlantic City. W. H. Kammerer, 33 East 61st Street, New York 21.

June 5: Society for Vascular Surgery, Atlantic City. George D. Lilly, 25 S. E. Second Avenue, Miami 32, Fla.

June 6–10: American Medical Association Annual Meeting, Atlantic City. Dr. George F. Lull, 535 North Dearborn Street, Chicago 10.

June 13–17: New Gordon Research Conference on Blood, Kimball Union Academy, Meriden, New Hampshire. Herbert L. Davis, Ph.D., Department of Biochemistry, University of Nebraska College of Medicine, Omaha 5.

ABROAD

April 27–30: Cardiologic Sessions of the Society of Physicians, Interns, Residents and Fellows of the Mexican National Cardiologic Institute, Mexico City. Dr. Jorge Soberón Acevedo, Secretary General, Avenida Cuahtemoc No. 300, Mexico City.

May 10: Eighth World Health Assembly, Mexico City. World Health Organization, Palais des Nations, Geneva, Switzerland.

May 23–26: International Surgical Congress, Geneva, Switzerland. Dr. Max Thorek, 1516 Lake Shore Drive, Chicago, Illinois.

May 26–31: Seventh International Congress of Comparative Pathology. Lausanne, Switzerland. Prof. Hauduroy, 19 Rue Cesar Roux, Lausanne.

June 13–17: American Pediatric Society, Quebec City, P.Q., Canada. A. C. McGuinness, 237 Medical Laboratory, University of Pennsylvania, Philadelphia.

June 13–17: European Congress on Rheumatism, The Hague, Netherlands. Dr. H. van Swaay, Pieter Bothstraat 12, The Hague.

June 15–18: American Society for Pediatric Research, Quebec City, P.Q., Canada. Sydney S. Gellis, 330 Brookline Avenue, Boston 15.

June 18–19: Fifth Congress of the International Association for the Study of the Bronchi. Stockholm, Sweden. Dr. Stahle, Kolmarsanatoriet, Sweden.

June 20–22: Canadian and British Medical Association, joint meeting. Toronto, Canada. Dr. Arthur D. Kelly, 244 St. George St., Toronto, Canada.

June 21–25: Commonwealth Health and Tuberculosis Conference, Royal Festival Hall, London, England. Mr. J. H. Harley Williams, Tavistock House North, Tavistock Square, London, W.C.1, England.

July 4–8: Congress of the International Diabetes Federation, Cambridge, England. James G. L. Jackson, Diabetic Association, 152 Harley St., London, W.1, England.

July 23–29: Sixteenth Congress of the International Society of Surgery. Copenhagen. Dr. L. Dejardin, 141 rue Delliard, Brussels, Belgium.

July 25–30: International Anatomical Congress, Paris, France. Prof. Gaston Cordier, 45 rue des Saints-Pères, Paris 6e, France.

July 25–30: International Federative Congress of Anatomy, Paris, France. 45 rue des Saints-Pères, Paris 6e, France.

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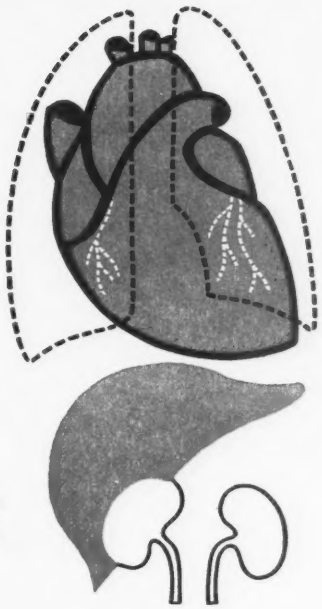

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Circulation

APRIL 1955
VOL. XI NO. 4

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

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